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CASE-FATALITY RATE IN 22Q11 MICRODELETION SYNDROME PATIENTS

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CASE-FATALITY RATE IN 22Q11 MICRODELETION SYNDROME PATIENTS

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ABSTRACT

Objective: Chromosome 22q11.2 deletion is the most common known microdeletion syndrome. Deaths related to the syndrome have been reported, but the magnitude of fatality has not been quantified. This study evaluated the impact of 22q11.2 deletion and its clinical manifestations in survival in a large cohort of Chilean patients with this syndrome.

Design: Analysis of demographic and clinical data of individuals with FISH- or MLPA-proven 22q11 deletions diagnosed between years 1998 and 2013 and comparison with national vital statistics. OR with 95% CI analysis was used to assess the association of clinical manifestations with fatality.

Setting: Genetic services in tertiary care centers in Chile following deleted patients from years 1998 to 2013.

Outcomes: Fatality rate

Results: Fifty nine of 419 patients (14.1%) were deceased during the study period, at a mean of 1.15 years, ranging from newborn to 32 years of age. Factors associated with fatality included the presence of congenital heart disease ($p < 0.0001$; OR 5.27; 95% CI 2.06-13.99), hypocalcemia ($p 0.002$, OR 4.272; 95% CI 1.67-11.15) and airway malacia ($p 0.002$, OR 13.37, 95% CI 1.19-110.51). Patients with the deletion and defects such as tetralogy of Fallot with or without pulmonary atresia, truncus arteriosus or ventricular septal defect had 2.6 to 4.6 fold higher fatality rate than that reported nationwide for the same types of defects.

Conclusions: In this cohort, we observed a fatality rate of 14.1%, implying that 1 every 7 patient with 22q11 deletion had died during the period of study. Significant association was observed with cardiac defects, hypocalcemia and airway malacia. Furthermore, fatality risk in patients with 22q11 deletion and cardiac defects exceeded the figures observed in Chile for children with structurally similar but isolated anomalies. This points to the need to identify the group of patients that may need specific perioperative management to improve survival.

ARTICLE SUMMARY

Strengths and limitations of the study

- The results are strengthened by the inclusion of a large group of patients with 22q11 deletion, most of them followed for over a decade, accounting for the majority of cases in the country and with similar access to congenital heart defect diagnosis and repair.
- The main limitation of our study is the dependance on clinical recognition and confirmation of the deletion: severe cases with early mortality and undiagnosed cases were not included.
- Another limitation is the partially complete data for some clinical variables, such as calcium levels, airway anatomy and immune function.

INTRODUCTION

Chromosome 22q11 microdeletion syndrome (22q11DS) (MIM #188400 and 192430) is the most common known microdeletion syndrome in humans, with an estimated incidence of 1 in 4000 live births¹. It is a cause of congenital heart disease (CHD), hypocalcemia, cognitive disabilities and psychiatric disease, among other features¹. Several authors have reported an increase in post-operative mortality in pediatric patients with CHD and 22q11DS, compared with those non-syndromic CHD^{2,3}, though this appears to be controversial and has not been found by other authors⁴⁻⁶. In addition, sudden death in adults with 22q11DS has also been described⁷. Given these findings, we sought to investigate survival and factors associated with general fatality in a large cohort of Chilean patients with this syndrome.

METHODS

Patients with 22q11DS confirmed by FISH (TUPLE 1 Probe, Abbott Molecular, Abbott Park, IL, USA) and/or MLPA (SALSA MLPA P250 DiGeorge probemix, MRC, Amsterdam, The Netherlands) from year 1998 to 2013, in the 6 clinical cytogenetic laboratories that

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3 perform such testing in Chile, were included in the study. Clinical and demographic data
4 were collected retrospectively from medical records and/or parental/patient interviews
5 using a standardized form from year 2013 and back to year 1998, when FISH testing was
6 introduced in clinical laboratories in the country. Death certificates were reviewed when
7 pertinent. The study was approved by the Institutional Review Board of participating
8 center, and patients or parents gave written informed consent.
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14 Association of demographic features and clinical manifestations with fatality was evaluated
15 using Fisher's exact test and odds ratio. Survival function was estimated using Kaplan-
16 Meier method. Statistical differences on the survival functions of CHD and non-CHD
17 patients were evaluated by the Log-rank test. For these analyses, the survival package
18 was used on the R software⁸. For some clinical features, data was incomplete; therefore
19 the statistical analysis was performed including only patients with recorded data. As a
20 reference, results were compared with official case fatality statistics from hospital
21 discharges in Chile for year 2010, the latest information available at the time of this writing
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^{9,10}. A p value < 0.05 was considered statistically significant.

RESULTS

Four hundred and nineteen patients (198 males, 47.2%) with postnatal diagnosis of the deletion gave informed consent to participate in the study, of 430 known patients. The median age was 12 years, ranging from 0 to 52 years. Fifty nine (14.1%) were deceased during the 16 years considered in this study (1998 to 2013). Mean age at death was 1.15 years, with a minimum of 1 day and a maximum of 32.4 years. In fact, only 2 patients died after 2 years of age, one at 9.9 years from septic shock and the one at 32.4 years, from pulmonary fibrosis and chronic respiratory insufficiency. Gender was not associated with fatality.

Information on cardiac anatomy was available on 366 patients, 87% of the total. Of them, 233 (63.7%) had CHD and 133 (36.3%) had structurally normal heart by echocardiogram. The presence of cardiac anomalies was significantly associated with mortality: 46 patients with CHD and 6 patients without died during the period of the study ($p < 0.0001$; OR 5.27; 95% CI 2.06-13.99). The presence of CHD was recorded in 88.5% of the deceased individuals, and it was the direct cause of death in 63% of them, followed by sepsis in 13%.

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3 Figure 1 shows Kaplan-Meier survival curves for deleted patients with and without CHD.
4 Neither one of the 2 patients that died after 2 years of age had a CHD.
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7 Considering specific heart defects, fatality rate was 50% among the 22 patients with
8 truncus arteriosus, 32% for the 75 patients with tetralogy of Fallot, 41% for the subgroup of
9 24 infants with tetralogy of Fallot and pulmonary atresia, and 4.2% for the 48 patients with
10 ventricular septal defects (VSD).
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14 As a reference for comparison, infant mortality in Chile was 7.9/1000 and fatality rate
15 related to CHD was 4.9% in 2010⁹. Half of these deaths occurred in infants one year of
16 age or younger. Fatality rates due to specific defects was 12% for truncus arteriosus, 7%
17 for tetralogy of Fallot and 1.6% for VSD. These figures are between 2.6-4.6 fold lower than
18 the fatality rates observed for the same structural defect in 22q11DS patients¹⁰.
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23 Other factors associated with early death were a history of hypocalcemia, measured as
24 total calcium ($p < 0.002$; OR 4.27; 95% CI 1.67-11.15) and airway malacia demonstrated by
25 bronchoscopy (OR 13.375; 95% CI 1.190-110.514), although the latter data was very
26 limited, and we presume that endoscopic studies were performed only on symptomatic
27 patients. Available information on immune function was insufficient for analysis. Clinical
28 features are summarized in Table 1.
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Table 1. Clinical characteristics of patients

	Deceased, n (%)	Alive, n (%)	TOTAL	p value	OR (95% CI)
Total	59 (14.1)	360 (85.8)	419		
Males	26 (44.1)	172 (47.8)	198	0.73	0.872 (0.481-1.578)
CHD data available	52 (88.5)	314 (87.2)	366		
With CHD (% with available data)	46 (77.9)	187 (59.5)	233	<0.0001	5.27 (2.056-13.994)
Calcium data available	24 (40.7)	253 (70.2)	277		
Hypocalcemia (% with available data)	15 (62.5)	71 (28.1)	86	0.002	4.272 (1.666-11.145)
Airway data available	6 (10.2)	246 (68.3)	252		
Malacia (% with available data)	4 (66.7)	32 (13.0)	36	0.002	13.375 (1.190-110.514)

DISCUSSION

Our observations confirm that patients with 22q11DS have high fatality rates: we found that 14.1 % of a large cohort of Chilean patients had died during the 16-year period of observation. This, to our knowledge, this is the largest series reporting case fatality rate and survival in this syndrome.

The majority of deaths occurred during the first year of life, these were associated with the presence of CHD, particularly with severe cardiac defects that are common in this syndrome, such as tetralogy Fallot with pulmonary atresia and truncus arteriosus. It has been previously proposed that right-sided heart failure, related to pulmonary vascular resistance, a common complication of these anomalies, is an important contributor to mortality^{3,11,12}.

Diagnosis and treatment of CHD has universal coverage under Chilean Health Care Reform¹³ since 2003, therefore it is unlikely that differences in local clinical practices are the main cause of the high mortality in deleted patients. We found that patients with 22q11DS showed higher fatality than the general statistics for patients with similar CHDs in Chile. This suggests the presence of additional risk factors in patients with the syndrome that may contribute to higher fatality. Among those, we found that hypocalcemia and airway abnormalities were also significant risk factors. Low calcium levels are common in patients with the deletion, particularly in the cardiac postoperative period. Shen et al¹¹ have described that the frequency of hypocalcemia and the speed of calcium level decline after surgery are higher in deleted than in non-deleted patients, and that this was associated with postsurgical complications. They did not show association of hypocalcemia with mortality as we did in our study, but this may be related to the smaller sample size in theirs (n=19). We did not have parathyroid hormone (PTH) levels recorded in our patients, but others have demonstrated that postoperative hypocalcemia is due to decreased PTH reserve^{11,14}. Our results emphasize the need to direct specific attention to calcium levels in the perioperative period of 22q11DS patients.

Airway malacia was also found to be risk factor for lethality. It can be due to extrinsic compression by aberrant vessels or due to intrinsic anomalies in these patients¹⁵, and its management often requires prolonged mechanical ventilation and increased risk for infection, which may also contribute to mortality. Future studies in pathogenesis, early

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3 detection and management strategies of airway anomalies in the syndrome will be relevant
4 for treatment and prognosis.
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7 Although limited by its retrospective nature, partially complete data and biases due to
8 underrecognition of an unknown proportion of patients with the deletion, this study
9 demonstrates that the presence of 22q11DS adversely affects survival, particularly in
10 individuals with CHD, hypocalcemia and airway malacia. There may be a need for
11 modified surgical techniques, timing and/or perioperative management of cardiac and
12 extracardiac manifestations, as proposed by Carotti et al ¹⁶ in order to improve survival in
13 22q11DS patients to make it at least comparable to their non-syndromic counterparts, as is
14 the current reality, for example, for patients with Down syndrome ¹⁷.
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24
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27

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31 **Contributions:** GMR and MLG participated in study concept and design.
32 MLG, MP, GL and PA participated in acquisition of data. HL and ID
33 performed the statistical analysis of the data. GMR, GL and CV and
34 DT participated in drafting and critical revision of the manuscript for
35 important intellectual content. FB and KE provided administrative, technical and material
36 support. GMR obtained funding and participated in overall study supervision. All authors
37 critically reviewed and approved the final version of the manuscript.
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44 **Data sharing:** no additional data are available
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48 REFERENCES

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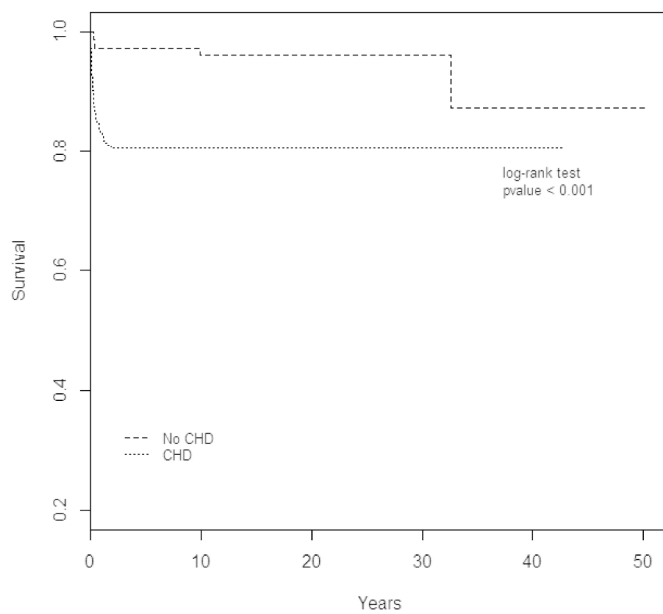
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Figure 1. Kaplan-Meier survival curves for 22q11DS patients with or without CHD



n, no CHD	133	91	31	15	7	1
n CHD	233	104	28	4	1	0
TOTAL	366	195	59	19	8	1

215x279mm (300 x 300 DPI)

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- The main limitation of our study is that it relies on clinical recognition and confirmation of the deletion, therefore severe cases with early mortality and undiagnosed cases are not included.
- We recognize that statistical analysis is also limited by partially complete data for some relevant clinical variables, such as calcium levels, airway anatomy and immune function.

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Chromosome 22q11 microdeletion syndrome (22q11DS) (MIM #188400 and 192430) is the most common known microdeletion syndrome in humans, with an estimated incidence of 1 in 4000 live births¹. It is a cause of congenital heart disease (CHD), hypocalcemia, cognitive disabilities and psychiatric disease, among other features¹. Several authors have reported an increase in post-operative mortality in pediatric patients with CHD and 22q11DS, compared with those with non-syndromic CHD^{2,3}, though this appears to be controversial and has not been found by other authors⁴⁻⁶. In addition, sudden death in adults with 22q11DS has also been described⁷. Given these findings, we sought to investigate survival and factors associated with fatality in a large cohort of Chilean patients with this syndrome.

METHODS

Patients with 22q11DS confirmed by FISH (TUPLE 1 Probe, Abbott Molecular, Abbott Park, IL, USA) and/or MLPA (SALSA MLPA P250 DiGeorge probemix, MRC, Amsterdam, The Netherlands) in the 6 clinical cytogenetic laboratories that perform such testing in Chile, were included in the study from year 1998 (when FISH testing was clinically introduced in the country) to 2013. Individuals were ascertained and followed through cardiology, cleft palate, genetics or developmental pediatrics clinics, family support groups and/or through periodic surveys to Cytogenetics laboratories. Clinical and demographic data were collected from medical records, death certificates when pertinent and/or parental/patient interviews using a standardized questionnaire. Information was gathered retrospectively at the time of inclusion and prospectively thereafter. Alive or deceased status at December 2013 was obtained for every participant through the National Civil and Information Registry (www.registrocivil.cl). This longitudinal cohort was recruited as part of consecutive research projects aimed at the characterization of the syndrome in Chile and at the identification of clinical, epidemiological and molecular risk factors for the development of individual features of the syndrome. The study was approved by the Institutional Review Boards of participating centers, and patients or parents gave written informed consent.

The association of demographic features and clinical manifestations with fatality was evaluated using Fisher's exact test and odds ratio. Survival function was estimated using Kaplan-Meier method. Statistical differences in the survival functions of CHD and non-CHD

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3 patients were evaluated by the Log-rank test. For some clinical features, data was
4 incomplete; therefore the statistical analysis was performed including only patients with
5 recorded data. As a reference, results were compared with official case fatality statistics for
6 congenital heart disease (ICD-10, codes Q20-25) from hospital discharges in Chile for
7 years 2001-2011, the latter being the most recent nation-wide information available at the
8 time of writing⁸. R software⁹ and SPSS version 20.0 (SPSS Inc, Chicago, IL) were used
9 for statistical analysis. A p value < 0.05 was considered statistically significant.
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15 16 17 18 **RESULTS**

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20 Of 430 known patients with postnatal diagnosis of the deletion, 419 gave consent to
21 participate in the study. There were 198 males (47.2%) and 221 females (52.7%).
22 Seventeen cases (4 %) were known to be inherited from a parent with the deletion, but this
23 is a clear underestimate since only parents with features suggestive of the syndrome had
24 molecular testing due to insurance coverage limitations.
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29 The median age of inclusion in the cohort was 12 years, ranging from 0 to 52 years. Fifty
30 nine (14.1%) died during the 15 years considered in this study (1998 to 2013). Median age
31 at death was 3.4 months, with a minimum of 3 days and a maximum of 32.4 years. In fact,
32 only 2 patients died after 2 years of age, one at 9.9 years from septic shock and the one at
33 32.4 years from pulmonary fibrosis and chronic respiratory insufficiency. Gender was not
34 associated with fatality.
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40 Causes of death documented in the death certificate are listed in Table 1. Cardiac cause
41 was the most common, listed as the single cause in 27 (45.8%) or in combination with
42 other causes in 46 (78%) patients. This was followed by infectious
43 causes/immunodeficiency (sepsis, pneumonia, or intra-abdominal source), listed as the
44 single primary cause in 7 patients (11.9%) or in combination with other (usually cardiac) in
45 14 (23%). The third most frequent cause of death was related to the respiratory system
46 (respiratory failure, malacia) alone in 2 patients (3.4%) or with other causes in 11 (18.6%).
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52 Information about cardiac anatomy was available for 366 patients, corresponding to 87%
53 of the total number of participants and 88.5% of the deceased. Of the 366, 233 (63.7%)
54 had a CHD and 133 (36.3%) had a structurally normal heart and great vessels by
55 echocardiogram. The presence of cardiac anomalies was significantly associated with
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3 mortality: 46 patients with CHD (19.7% of those with CHD) and 6 patients without (4.5% of
4 those without CHD) died during the period of the study (OR 5.27; 95% CI 2.06-13.99;
5 $p < 0.0001$) (Table 2). Figure 1 shows Kaplan-Meier survival curves for deleted patients with
6 and without CHD. The 2 patients that died after 2 years of age did not have CHD.
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10 Information regarding cardiac surgery was available for 40 of the 46 deceased patients
11 with known CHD (87%). Of the 40 with surgical information, 10 (25%) died before
12 operative repair, 3 (7.5%) died during surgery and 27 (67.5%) died after surgery. Patients
13 with CHD who underwent surgical repair died at a mean of 6 months (range 11 days to
14 1.65 years), whereas those with CHD but no cardiac surgery had earlier deaths, with a
15 mean of 1 month and ranging from 3 days to 3.7 months of age. The 6 patients without
16 CHD died at a mean of 7 years, ranging from 2.8 months to 32.4 years. In contrast, data
17 on surgery was available for 186 of 187 (99%) of patients with CHD that were alive in
18 December 2013. One hundred and forty (75%) of them had surgical repair, similar to the
19 deceased group. The rest ($n=46$) had pending surgeries or had anatomical defects that did
20 not require intervention (small ASDs or VSDs, right sided aortic arch or aberrant
21 subclavian arteries).
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31 As a reference for comparison, infant mortality in Chile was approximately 8.0 /1000 live
32 births in the past decade. The national fatality rate among hospital discharges for CHD
33 was, on average, 5.4 % from 2001 to 2011. Eighty six percent of these deaths occurred in
34 infants one year of age or younger, similar to the patients with 22q11 deletion. Since the
35 deaths in both groups with CHD (general and 22q11DS), were concentrated on the first
36 year of life, we compared case fatality rates for hospital discharges for CHD in infants 1
37 year of age or younger, from 2001 to 2011. We found that, on average, fatalities were 3.6-
38 fold higher in infants with 22q11DS than the rate reported for CHD nation-wide (Table 3).
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45 Given that the types of CHD in patients with 22q11DS tend to be more severe than those
46 seen in apparently isolated cases, we compared fatality rates for specific cardiac defects
47 that are common in the syndrome. We found that, in patients with 22q11DS, fatality rate
48 was 50% among the 22 patients with truncus arteriosus, 32% for the 75 patients with
49 tetralogy of Fallot, 41% for the subgroup of 24 infants with tetralogy of Fallot and
50 pulmonary atresia, and 4.2% for the 48 patients with ventricular septal defects (VSD). In
51 comparison, the average case fatality rates for Chilean patients were 12% for truncus
52 arteriosus, 7% for tetralogy of Fallot and 1.6% for VSD⁹. The latter figures are between
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3 2.6-4.6 fold lower than the fatality rates observed for the same structural defect in
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5 22q11DS patients.
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8 Other factors associated with early death were a history of hypocalcemia, measured as
9 total calcium ($p=0.001$; OR 4.27; 95% CI 1.67-11.15) and airway malacia demonstrated by
10 bronchoscopy ($p=0.043$; OR 13.375; 95% CI 1.190-110.514), although the latter data
11 were very limited, since endoscopic studies were performed only on symptomatic patients.
12 Available information on immune and thyroid function was insufficient for analysis.
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Table 1. Cause of death according to the death certificate

	n	%
Cardiac	27	45.8
Cardiac + respiratory failure	9	15.3
Cardiac + infectious	6	10.2
Cardiac + central nervous system anomaly	2	3.4
Cardiac + immunodeficiency	1	1.7
Cardiac + multisystem failure	1	1.7
Infection (pneumonia) or sepsis	7	11.9
Multisystem failure	2	3.4
Respiratory failure	1	1.7
Tracheobroncho malacia	1	1.7
Central nervous system anomaly	1	1.7
Unknown	1	1.7
TOTAL	59	100.0

Table 2. Clinical characteristics of patients

Characteristic		Deceased, n (%)	Alive, n (%)	TOTAL	p value (Fisher's exact test)	OR (95% CI) deceased vs. alive patients
		59 (14.1)	360 (85.8)	419		
Gender	Males	26 (44.1)	172 (47.8)	197	0,67	0.87(0.48-1.58)
	Females	33 (55.9)	188 (52.2)	221		
Cardiac status	With CHD data available	52 (14.2)	314 (85.8)	366	<0.0001	5.27 (2.06-13.99)
	With CHD	46 (88.5)	187 (59.5)	233		
	Normal cardiac anatomy	6 (11.5)	127 (40.5)	133		
Calcium status	With calcium data available	24	253	277	0.001	4.27(1.67-11.15)
	Hypocalcemia	15 (62.5)	71 (28.1)	86		
	Normal calcium	9 (37.5)	182 (71.2)	141		
Airway status	With airway data available	6	246	252	0,0043	13.38 (1.19-110.51)
	Malacia	4 (67)	32 (13)	36		
	Normal airway	2 (33)	214 (87)	216		

Table 3. Case fatality rates for hospital discharges in infants 1 year or younger with CHD: comparison of patients with 22q11DS and general national data (ICD 10 codes Q20-Q25).

Birth year	Case fatality rates in 22q11DS patients with CHD (per 100 cases)	General case fatality rate for CHD in Chile (per 100 cases)⁹	Ratio of case fatality for CHD in 22q11DS/general
2001	28.57	6.63	4.31
2002	18.18	8.53	2.13
2003	0.00	7.77	0.00
2004	23.81	9.29	2.56
2005	21.43	9.30	2.30
2006	30.00	6.79	4.42
2007	41.67	7.59	5.49
2008	29.41	6.63	4.43
2009	42.11	8.55	4.92
2010	33.33	6.78	4.92
2011	42.86	7.49	5.72
Average	28.31	7.75	3.65

DISCUSSION

Our observations confirm that patients with 22q11DS have high fatality rates: we found that 14.1 %, or 1 in 7 patients, of a large cohort of Chilean patients died during the 15-year period of observation. For the subgroup of patients with the deletion and CHD, fatality rate was 19.7%, or almost one 1 in 5 patients. To our knowledge, this is the largest series reporting case fatality rate and survival in this syndrome.

The majority of deaths occurred during the first year of life. These were associated with the presence of CHD, particularly with severe cardiac defects that are common in this syndrome, such as tetralogy Fallot with pulmonary atresia and truncus arteriosus. It has been proposed that right-sided heart failure, related to pulmonary vascular resistance, a common complication of these anomalies, is an important contributor to mortality^{3,10,11}.

Diagnosis and treatment of CHD has universal coverage under Chilean Health Care Reform¹², and pediatric cardiac surgeries have been performed in 3 national referral centers since 2005. Therefore, it is unlikely that differences in local clinical practices are the main cause of the high mortality in patients with 22q11DS, at least in the past 8 years. In fact, similar figures are observed when comparing fatality rates before and after the implementation of universal coverage for diagnosis and treatment of CHD, guaranteed after the reform. Although overall national infant mortality for CHDs decreased in this period⁹, the impact of universal coverage appears to be less evident for children with severe and complex defects such as those that are seen in patients with 22q11DS. Indeed, we found that patients with 22q11DS had a higher overall fatality rate than the national statistics for patients with similar CHDs, and that this was evident for specific cardiac defects that are common in the syndrome, such as tetralogy of Fallot, truncus arteriosus and VSD. This suggests that, even for similar anatomic defects, there are additional manifestations and probably other pathophysiologic features in patients with the syndrome that may contribute to higher fatality than in cases of apparently isolated defects. Among these, we found that hypocalcemia and airway abnormalities were also significant risk factors associated with early death. Low calcium levels are common in patients with the deletion, particularly in the cardiac postoperative period. Shen et al¹⁰ described that frequency of hypocalcemia and the speed of calcium level decline after surgery is higher in patients with the deletion than in those without, and that this is associated with postsurgical complications. They did not show association of hypocalcemia with mortality as we did in this study, but this may be related to their smaller

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3 sample size (n=19). We did not have parathyroid hormone (PTH) levels for our patients,
4 but others have demonstrated that postoperative hypocalcemia is due to decreased PTH
5 reserve ^{10,13}. Our results emphasize a need to direct specific attention to calcium levels in
6 the perioperative period of 22q11DS patients.
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10 Airway malacia was also found to be a risk factor for lethality. It can be due to extrinsic
11 compression by aberrant vessels or due to intrinsic anomalies in these patients¹⁴, and its
12 management often requires prolonged mechanical ventilation which brings an increased
13 risk of infection that may also contribute to mortality. Future studies in the pathogenesis,
14 early detection and management strategies of airway anomalies in the syndrome will be
15 relevant for treatment and prognosis.
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19 This study is limited by its retrospective nature, partially complete data and biases due to
20 underrecognition of an unknown proportion of patients with the deletion. Nevertheless, in
21 this relatively large series of patients, we found that the presence of 22q11DS adversely
22 affects survival, particularly in individuals with CHD, hypocalcemia and/or airway malacia.
23 There may be a need for modified surgical techniques, timing and/or perioperative
24 management of cardiac and extracardiac manifestations, as proposed by Carotti et al ¹⁵ in
25 order to improve survival in 22q11DS patients and make it at least comparable to their
26 non-syndromic counterparts, as is the current reality, for example, for patients with Down
27 syndrome ¹⁶.
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6

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11

12 **Contributions:** GMR and MLG participated in study concept and design.
13 MLG, MP, GL and PA participated in acquisition of data. ID and HL
14 performed the statistical analysis. GMR, GL and CV and
15 PA participated in drafting and critical revision of the manuscript for important intellectual
16 content. FB and KE provided administrative, technical and material support. GMR obtained
17 funding and participated in overall study supervision. All authors critically reviewed and
18 approved the final version of the manuscript.
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25 **Data sharing:** No additional data are available
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CASE-FATALITY RATE IN 22Q11 MICRODELETION SYNDROME PATIENTS

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ABSTRACT

Objective: Chromosome 22q11.2 deletion is the most common known microdeletion syndrome. Deaths related to the syndrome have been reported, but the magnitude of fatality has not been quantified. This study evaluated the impact on survival of 22q11.2 deletion and its clinical manifestations in a large cohort of Chilean patients with this syndrome.

Design: Demographic and clinical data of individuals with FISH- or MLPA-proven 22q11 deletions diagnosed between years 1998 and 2013 were analyzed and compared with national vital statistics. OR with 95% CI analysis was used to assess the association of clinical manifestations with fatality.

Setting: Genetic services in tertiary care centers in Chile following patients with 22q11.2 deletion from years 1998 to 2013.

Outcomes: Fatality rate

Results: Fifty nine of 419 patients (14.1%) died during the study period, at a median of 3.4 months, ranging from newborn to 32 years of age. Factors associated with fatality included congenital heart disease (OR 5.27; 95% CI 2.06-13.99 p<0.0001), hypocalcemia (OR 4.27; 95% CI 1.67-11.15; p 0.002) and airway malacia (OR 13.37; 95% CI 1.19-110.51; p 0.002). Patients with deletion and defects such as tetralogy of Fallot with or without pulmonary atresia, truncus arteriosus or ventricular septal defect had 2.6 to 4.6 fold higher fatality rate than that reported nationwide for the same types of defects.

Conclusions: In this cohort, we observed a fatality rate of 14.1%, implying that 1 in 7 patients with 22q11 deletion died during the period of study. Significant association was observed with cardiac defects, hypocalcemia and airway malacia. Furthermore, fatality risk in patients with 22q11 deletion and cardiac defects exceeded the global figures observed in Chile for infants with structurally similar but apparently isolated anomalies. These observations point to a need to identify the group of patients that may require specific perioperative management to improve survival.

ARTICLE SUMMARY

Strengths and limitations of the study

- The results are strengthened by the inclusion of a large group of patients with 22q11 deletion, most of them followed for over a decade, accounting for the majority of cases in the country and with similar access to congenital heart defect diagnosis and repair since 2005 in the context of the National Health Care Reform.
- The main limitation of our study is that it relies on clinical recognition and confirmation of the deletion, therefore severe cases with early mortality and undiagnosed cases are not included.
- We recognize that **statistical analysis** is also limited by partially complete data for some relevant clinical variables, such as calcium levels, airway anatomy and immune function.

INTRODUCTION

Chromosome 22q11 microdeletion syndrome (22q11DS) (MIM #188400 and 192430) is the most common known microdeletion syndrome in humans, with an estimated incidence of 1 in 4000 live births ¹. It is a cause of congenital heart disease (CHD), hypocalcemia, cognitive disabilities and psychiatric disease, among other features ¹. Several authors have reported an increase in post-operative mortality in pediatric patients with CHD and 22q11DS, compared with those with non-syndromic CHD ^{2,3}, though this appears to be controversial and has not been found by other authors ⁴⁻⁶. In addition, sudden death in adults with 22q11DS has also been described ⁷. Given these findings, we sought to investigate survival and factors associated with fatality in a large cohort of Chilean patients with this syndrome.

METHODS

Patients with 22q11DS confirmed by FISH (TUPLE 1 Probe, Abbott Molecular, Abbott Park, IL, USA) and/or MLPA (SALSA MLPA P250 DiGeorge probemix, MRC, Amsterdam, The Netherlands) in the 6 clinical cytogenetic laboratories that perform such testing in Chile, were included in the study from year 1998 **(when FISH testing was clinically introduced in the country) to 2013. Individuals were ascertained and followed through cardiology, cleft palate, genetics or developmental pediatrics clinics, family support groups and/or through periodic surveys to Cytogenetics laboratories. Clinical and demographic**

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3 data were collected from medical records, death certificates when pertinent and/or
4 parental/patient interviews using a standardized questionnaire. Information was gathered
5 retrospectively at the time of inclusion and prospectively thereafter. Alive or deceased
6 status at December 2013 was obtained for every participant through the National Civil and
7 Information Registry (www.registrocivil.cl). This longitudinal cohort was recruited as part of
8 consecutive research projects aimed at the characterization of the syndrome in Chile and
9 at the identification of clinical, epidemiological and molecular risk factors for the
10 development of individual features of the syndrome. The study was approved by the
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20 The association of demographic features and clinical manifestations with fatality was
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22 Kaplan-Meier method. Statistical differences in the survival functions of CHD and non-CHD
23 patients were evaluated by the Log-rank test. For some clinical features, data was
24 incomplete; therefore the statistical analysis was performed including only patients with
25 recorded data. As a reference, results were compared with official case fatality statistics for
26 congenital heart disease (ICD-10, codes Q20-25) from hospital discharges in Chile for
27 years 2001-2011, the latter being the most recent nation-wide information available at the
28 time of writing⁸. R software⁹ and SPSS version 20.0 (SPSS Inc, Chicago, IL) were used
29 for statistical analysis. A p value < 0.05 was considered statistically significant.
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40 RESULTS

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42 Of 430 known patients with postnatal diagnosis of the deletion, 419 gave consent to
43 participate in the study. There were 198 males (47.2%) and 221 females (52.7%).
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32.4 years from pulmonary fibrosis and chronic respiratory insufficiency. Gender was not associated with fatality.

Causes of death documented in the death certificate are listed in Table 1. Cardiac cause was the most common, listed as the single cause in 27 (45.8%) or in combination with other causes in 46 (78%) patients. This was followed by infectious causes/immunodeficiency (sepsis, pneumonia, or intra-abdominal source), listed as the single primary cause in 7 patients (11.9%) or in combination with other (usually cardiac) in 14 (23%). The third most frequent cause of death was related to the respiratory system (respiratory failure, malacia) alone in 2 patients (3.4%) or with other causes in 11 (18.6%).

Information about cardiac anatomy was available for 366 patients, corresponding to 87% of the total number of participants and 88.5% of the deceased. Of the 366, 233 (63.7%) had a CHD and 133 (36.3%) had a structurally normal heart and great vessels by echocardiogram. The presence of cardiac anomalies was significantly associated with mortality: 46 patients with CHD (19.7% of those with CHD) and 6 patients without (4.5% of those without CHD) died during the period of the study (OR 5.27; 95% CI 2.06-13.99; $p < 0.0001$) (Table 2). Figure 1 shows Kaplan-Meier survival curves for deleted patients with and without CHD. The 2 patients that died after 2 years of age did not have CHD.

Information regarding cardiac surgery was available for 40 of the 46 deceased patients with known CHD (87%). Of the 40 with surgical information, 10 (25%) died before operative repair, 3 (7.5%) died during surgery and 27 (67.5%) died after surgery. Patients with CHD who underwent surgical repair died at a mean of 6 months (range 11 days to 1.65 years), whereas those with CHD but no cardiac surgery had earlier deaths, with a mean of 1 month and ranging from 3 days to 3.7 months of age. The 6 patients without CHD died at a mean of 7 years, ranging from 2.8 months to 32.4 years. In contrast, data on surgery was available for 186 of 187 (99%) of patients with CHD that were alive in December 2013. One hundred and forty (75%) of them had surgical repair, similar to the deceased group. The rest ($n=46$) had pending surgeries or had anatomical defects that did not require intervention (small ASDs or VSDs, right sided aortic arch or aberrant subclavian arteries).

As a reference for comparison, infant mortality in Chile was approximately 8.0 /1000 live births in the past decade. The national fatality rate among hospital discharges for CHD was, on average, 5.4 % from 2001 to 2011. Eighty six percent of these deaths occurred in

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3 infants one year of age or younger, similar to the patients with 22q11 deletion. Since the
4 deaths in both groups with CHD (general and 22q11DS), were concentrated on the first
5 year of life, we compared case fatality rates for hospital discharges for CHD in infants 1
6 year of age or younger, from 2001 to 2011. We found that, on average, fatalities were 3.6-
7 fold higher in infants with 22q11DS than the rate reported for CHD nation-wide (Table 3).

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12 Given that the types of CHD in patients with 22q11DS tend to be more severe than those
13 seen in apparently isolated cases, we compared fatality rates for specific cardiac defects
14 that are common in the syndrome. We found that, in patients with 22q11DS, fatality rate
15 was 50% among the 22 patients with truncus arteriosus, 32% for the 75 patients with
16 tetralogy of Fallot, 41% for the subgroup of 24 infants with tetralogy of Fallot and
17 pulmonary atresia, and 4.2% for the 48 patients with ventricular septal defects (VSD). In
18 comparison, the average case fatality rates for Chilean patients were 12% for truncus
19 arteriosus, 7% for tetralogy of Fallot and 1.6% for VSD⁹. The latter figures are between
20 2.6-4.6 fold lower than the fatality rates observed for the same structural defect in
21 22q11DS patients.

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29 Other factors associated with early death were a history of hypocalcemia, measured as
30 total calcium ($p=0.001$; OR 4.27; 95% CI 1.67-11.15) and airway malacia demonstrated by
31 bronchoscopy ($p=0.043$; OR 13.375; 95% CI 1.190-110.514), although the latter data
32 were very limited, since endoscopic studies were performed only on symptomatic patients.
33 Available information on immune and thyroid function was insufficient for analysis.
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Table 1. Cause of death according to the death certificate

	n	%
Cardiac	27	45.8
Cardiac + respiratory failure	9	15.3
Cardiac + infectious	6	10.2
Cardiac + central nervous system anomaly	2	3.4
Cardiac + immunodeficiency	1	1.7
Cardiac + multisystem failure	1	1.7
Infection (pneumonia) or sepsis	7	11.9
Multisystem failure	2	3.4
Respiratory failure	1	1.7
Tracheobroncho malacia	1	1.7
Central nervous system anomaly	1	1.7
Unknown	1	1.7
TOTAL	59	100.0

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Table 2. Clinical characteristics of patients

Characteristic		Deceased, n (%)	Alive, n (%)	TOTAL	p value (Fisher's exact test)	OR (95% CI) deceased vs. alive patients
		59 (14.1)	360 (85.8)	419		
Gender	Males	26 (44.1)	172 (47.8)	197	0,67	0.87(0.48-1.58)
	Females	33 (55.9)	188 (52.2)	221		
Cardiac status	With CHD data available	52 (14.2)	314 (85.8)	366	<0.0001	5.27 (2.06-13.99)
	With CHD	46 (88.5)	187 (59.5)	233		
	Normal cardiac anatomy	6 (11.5)	127 (40.5)	133		
Calcium status	With calcium data available	24	253	277	0.001	4.27(1.67-11.15)
	Hypocalcemia	15 (62.5)	71 (28.1)	86		
	Normal calcium	9 (37.5)	182 (71.2)	141		
Airway status	With airway data available	6	246	252	0,0043	13.38 (1.19-110.51)
	Malacia	4 (67)	32 (13)	36		
	Normal airway	2 (33)	214 (87)	216		

Table 3. Case fatality rates for hospital discharges in infants 1 year or younger with CHD: comparison of patients with 22q11DS and general national data (ICD 10 codes Q20-Q25).

Birth year	Case fatality rates in 22q11DS patients with CHD (per 100 cases)	General case fatality rate for CHD in Chile (per 100 cases) ⁹	Ratio of case fatality for CHD in 22q11DS/general
2001	28.57	6.63	4.31
2002	18.18	8.53	2.13
2003	0.00	7.77	0.00
2004	23.81	9.29	2.56
2005	21.43	9.30	2.30
2006	30.00	6.79	4.42
2007	41.67	7.59	5.49
2008	29.41	6.63	4.43
2009	42.11	8.55	4.92
2010	33.33	6.78	4.92
2011	42.86	7.49	5.72
Average	28.31	7.75	3.65

DISCUSSION

Our observations confirm that patients with 22q11DS have high fatality rates: we found that 14.1 %, or 1 in 7 patients, of a large cohort of Chilean patients died during the 15-year period of observation. For the subgroup of patients with the deletion and CHD, fatality rate was 19.7%, or almost one 1 in 5 patients. To our knowledge, this is the largest series reporting case fatality rate and survival in this syndrome.

The majority of deaths occurred during the first year of life. These were associated with the presence of CHD, particularly with severe cardiac defects that are common in this syndrome, such as tetralogy Fallot with pulmonary atresia and truncus arteriosus. It has been proposed that right-sided heart failure, related to pulmonary vascular resistance, a common complication of these anomalies, is an important contributor to mortality^{3,10,11}.

Diagnosis and treatment of CHD has universal coverage under Chilean Health Care Reform¹², and pediatric cardiac surgeries have been performed in 3 national referral centers since 2005. Therefore, it is unlikely that differences in local clinical practices are the main cause of the high mortality in patients with 22q11DS, at least in the past 8 years.

In fact, similar figures are observed when comparing fatality rates before and after the implementation of universal coverage for diagnosis and treatment of CHD, guaranteed after the reform. Although overall national infant mortality for CHDs decreased in this period⁹, the impact of universal coverage appears to be less evident for children with severe and complex defects such as those that are seen in patients with 22q11DS.

Indeed, we found that patients with 22q11DS had a higher overall fatality rate than the national statistics for patients with similar CHDs, and that this was evident for specific cardiac defects that are common in the syndrome, such as tetralogy of Fallot, truncus arteriosus and VSD. This suggests that, even for similar anatomic defects, there are additional manifestations and probably other pathophysiologic features in patients with the syndrome that may contribute to higher fatality than in cases of apparently isolated defects. Among these, we found that hypocalcemia and airway abnormalities were also significant risk factors associated with early death. Low calcium levels are common in patients with the deletion, particularly in the cardiac postoperative period. Shen et al¹⁰ described that frequency of hypocalcemia and the speed of calcium level decline after surgery is higher in patients with the deletion than in those without, and that this is associated with postsurgical complications. They did not show association of hypocalcemia with mortality as we did in this study, but this may be related to their smaller

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3 sample size (n=19). We did not have parathyroid hormone (PTH) levels for our patients,
4 but others have demonstrated that postoperative hypocalcemia is due to decreased PTH
5 reserve^{10,13}. Our results emphasize a need to direct specific attention to calcium levels in
6 the perioperative period of 22q11DS patients.
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10 Airway malacia was also found to be a risk factor for lethality. It can be due to extrinsic
11 compression by aberrant vessels or due to intrinsic anomalies in these patients¹⁴, and its
12 management often requires prolonged mechanical ventilation which brings an increased
13 risk of infection that may also contribute to mortality. Future studies in the pathogenesis,
14 early detection and management strategies of airway anomalies in the syndrome will be
15 relevant for treatment and prognosis.
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19 This study is limited by its retrospective nature, partially complete data and biases due to
20 underrecognition of an unknown proportion of patients with the deletion. Nevertheless, in
21 this relatively large series of patients, we found that the presence of 22q11DS adversely
22 affects survival, particularly in individuals with CHD, hypocalcemia and/or airway malacia.
23 There may be a need for modified surgical techniques, timing and/or perioperative
24 management of cardiac and extracardiac manifestations, as proposed by Carotti et al¹⁵ in
25 order to improve survival in 22q11DS patients and make it at least comparable to their
26 non-syndromic counterparts, as is the current reality, for example, for patients with Down
27 syndrome¹⁶.
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44 **Contributions:** GMR and MLG participated in study concept and design.
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47
48 MLG, MP, GL and PA participated in acquisition of data. ID and HL
49 performed the statistical analysis. GMR, GL and CV and
50 PA participated in drafting and critical revision of the manuscript for important intellectual
51 content. FB and KE provided administrative, technical and material support. GMR obtained
52 funding and participated in overall study supervision. All authors critically reviewed and
53 approved the final version of the manuscript.
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Data sharing: No additional data are available

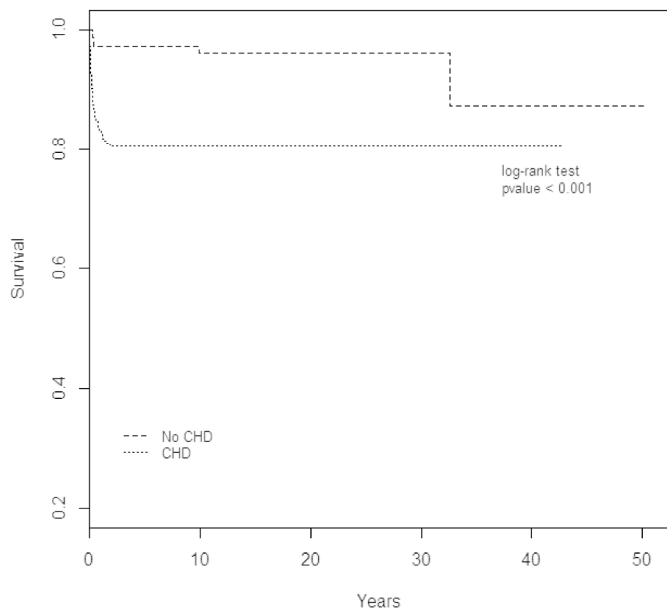
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Figure 1. Kaplan-Meier survival curves for 22q11DS patients with or without CHD



n, no CHD	133	91	31	15	7	1
n CHD	233	104	28	4	1	0
TOTAL	366	195	59	19	8	1

215x279mm (300 x 300 DPI)

BMJ Open

CASE-FATALITY RATE AND ASSOCIATED FACTORS IN 22Q11 MICRODELETION SYNDROME PATIENTS: A RETROSPECTIVE COHORT STUDY

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3 **CASE-FATALITY RATE AND ASSOCIATED FACTORS IN 22Q11 MICRODELETION**
4 **SYNDROME PATIENTS: A RETROSPECTIVE COHORT STUDY**
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3 Keywords: 22q11 deletion syndrome, congenital heart disease, DiGeorge syndrome,
4 fatality rate, hypocalcemia.
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For peer review only

ABSTRACT

Objective: Chromosome 22q11.2 deletion is the most commonly occurring known microdeletion syndrome. Deaths related to the syndrome have been reported, but the magnitude of fatality has not been quantified. This study evaluated the deletion's impact on survival and its clinical manifestations in a large cohort of Chilean patients.

Design: Demographic and clinical data of individuals with FISH- or MLPA-proven 22q11 deletions diagnosed between 1998 and 2013 were collected from medical records and death certificates. Case-fatality rate was calculated and compared with national vital statistics. OR with 95% CI analysis was used to assess the association between clinical manifestations and fatality.

Setting: Genetic services in tertiary care centers in Chile that were following patients with 22q11.2 deletion.

Outcomes: Fatality rate and associated factors

Results: Fifty-nine of 419 patients (14.1%) died during the study period, at a median of 3.4 months and ranging from 0 to 32 years of age. Factors associated with fatality included congenital heart disease (OR 5.27; 95% CI 2.06-13.99; $p < 0.0001$), hypocalcemia (OR 4.27; 95% CI 1.67-11.15; $p < 0.002$) and airway malacia (OR 13.37; 95% CI 1.19-110.51; $p < 0.002$). Patients with deletions and defects such as tetralogy of Fallot with or without pulmonary atresia, truncus arteriosus or ventricular septal defect, had a 2.6- to 4.6-fold higher fatality rate compared with nationwide reports for the same types of defects.

Conclusions: In this cohort, we observed a fatality rate of 14.1%, implying that 1 in 7 patients with 22q11 deletion died during the study period. Significant associations with cardiac defects, hypocalcemia and airway malacia were observed. Furthermore, the fatality risk in patients with 22q11 deletion and cardiac defects exceeded the global figures observed in Chile for infants with structurally similar but apparently isolated anomalies. These observations indicate a need to identify patients who may require specific perioperative management to improve survival.

ARTICLE SUMMARY

Strengths and limitations of the study

- The results are strengthened by the inclusion of a large group of patients with 22q11 deletion, most of whom were followed for over a decade. The sample accounts for the majority of cases in the country, and the participants have had similar access to congenital heart defect diagnosis and repair since 2005 in the context of the National Health Care Reform in Chile.
- The main limitation of our study is that it relied on clinical recognition and confirmation of the deletion; therefore, severe cases with early mortality and undiagnosed cases were not included.
- We recognize that statistical analysis is also limited by partially complete data for some relevant clinical variables, such as calcium levels, airway anatomy and immune function.

INTRODUCTION

Chromosome 22q11 microdeletion syndrome (22q11DS; MIM #188400 and 192430) is the most common known microdeletion syndrome in humans, with an estimated incidence of 1 in 4000 live births¹. It causes congenital heart disease (CHD), hypocalcemia, cognitive disabilities and psychiatric disease, among other symptoms¹. Several authors have reported an increase in post-operative mortality in pediatric patients with CHD and 22q11DS compared with patients with non-syndromic CHD^{2,3}; however, this association appears to be controversial and has not been observed by other authors⁴⁻⁶. In addition, sudden death in adults with 22q11DS has also been described⁷. Given these findings, we sought to investigate survival and factors associated with fatality in a large cohort of Chilean patients with this syndrome.

METHODS

Patients with 22q11DS that was confirmed with FISH (TUPLE 1 Probe, Abbott Molecular, Abbott Park, IL, USA) and/or MLPA (SALSA MLPA P250 DiGeorge probe mix, MRC, Amsterdam, The Netherlands) in one of the 6 clinical cytogenetic laboratories that perform such testing in Chile between 1998 (when FISH testing was clinically introduced in the country) and 2013 were included in the study. The patients were identified at cardiology, cleft palate, genetics or developmental pediatrics clinics; through family support groups; and/or through periodic surveys to cytogenetics laboratories. Clinical and demographic data were collected from medical records, death certificates when pertinent and/or parental/patient interviews using a standardized questionnaire. Information was gathered retrospectively at the time of inclusion and prospectively thereafter. Living or deceased status in December 2013 was obtained for every participant through the National Civil and Information Registry (www.registrocivil.cl). This longitudinal cohort was recruited as part of consecutive research projects that aim to characterize the syndrome in Chile and identify the clinical, epidemiological and molecular risk factors for the development of individual features of the syndrome. The study was approved by the institutional review boards of the participating centers, and the patients or their parents gave written informed consent.

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3 Cardiac anatomy was evaluated by a pediatric cardiologist using echocardiogram. Airway
4 abnormalities were assessed with bronchoscopy performed by a pediatric pulmonologist,
5 and malacia was defined as the collapse of at least 50% of the airway lumen during
6 expiration, cough or spontaneous breathing or a < 3:1 ratio of cartilage to membranous
7 wall area ⁸.

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12 The association of demographic features and clinical manifestations with fatality was
13 evaluated using Fisher's exact test and odds ratios. Survival function was estimated using
14 the Kaplan-Meier method. Significant differences in the survival functions of CHD and non-
15 CHD patients were evaluated with the log-rank test. For some clinical features, data were
16 incomplete; therefore, the statistical analysis included only patients with recorded data. As
17 a reference, the results were compared with official case fatality statistics for congenital
18 heart disease (ICD-10, codes Q20-25) from hospital discharges in Chile for 2001-2011, the
19 latter year being the most current nationwide information available at the time of writing ⁹.
20 R software ¹⁰ and SPSS version 20.0 (SPSS Inc., Chicago, IL) were used for statistical
21 analysis. A p value <0.05 was considered statistically significant.
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32 RESULTS

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34 Of 430 known patients with postnatal diagnosis of the deletion, 419 consented to
35 participate in the study. The participants included 198 males (47.2%) and 221 females
36 (52.7%). Seventeen cases (4%) had a parent with the deletion, but this prevalence is a
37 clear underestimate because only those parents with features suggestive of the syndrome
38 had undergone molecular testing because of insurance coverage limitations. Sixteen of
39 them (94%) were of maternal inheritance.
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45 The median age of inclusion in the cohort was 12 years and ranged from 0 to 52 years.
46 Fifty-nine (14.1%) participants died during the 15-year study period (1998 to 2013). The
47 median age at death was 3.4 months, with a minimum of 3 days and a maximum of 32.4
48 years. Only 2 patients died after 2 years of age: one at 9.9 years from septic shock and
49 one at 32.4 years from pulmonary fibrosis and chronic respiratory insufficiency. Gender
50 was not associated with fatality.
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55 1 lists the causes of death according to the death certificate. Cardiac causes were the
56 most common; they were listed as the single cause of death in 27 patients (45.8%) or in
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3 combination with other causes in 46 (78%) patients. Infectious causes/immunodeficiency
4 (sepsis, pneumonia, or intra-abdominal source) were the second most common cause of
5 death: they were listed as the single primary cause in 7 patients (11.9%) or in combination
6 with other causes (usually cardiac) in 14 patients (23.7%). The third most common cause
7 of death was related to the respiratory system (respiratory failure, malacia) alone in 2
8 patients (3.4%) or with other causes in 11 patients (18.6%).
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14 Information about cardiac anatomy was available for 366 patients, corresponding to 87%
15 of the total participants and 88.5% of the deceased. Of the 366 patients for whom cardiac
16 anatomy information was available, 233 (63.7%) had a CHD, and 133 (36.3%) had a
17 structurally normal heart and great vessels according to echocardiogram. The presence of
18 cardiac anomalies was significantly associated with mortality: 46 patients with CHD (19.7%
19 of all patients with CHD) and 6 patients without (4.5% of all patients without CHD) died
20 during the study period (OR 5.27; 95% CI 2.06-13.99; $p < 0.0001$; Table 2). Figure 1
21 compares Kaplan-Meier survival curves for the patients with and without CHD. The 2
22 patients who died after 2 years of age did not have CHD.
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30 Information regarding cardiac surgery was available for 40 of the 46 deceased patients
31 with known CHD (87%). Of the 40 deceased patients with surgical information, 10 (25%)
32 died before operative repair, 3 (7.5%) died during surgery, and 27 (67.5%) died after
33 surgery. Patients with CHD who underwent surgical repair died at a median of 3.5 months
34 of age (range 11 days to 1.65 years of age). These deaths occurred at a median of 3.6
35 months after surgery, ranging from 1 day to 1.2 years. Those with CHD but no cardiac
36 surgery died earlier, at a median of 0.2 months, ranging from 3 days to 3.7 months of age.
37 The 6 patients without CHD died at a median of 4.7 months, ranging from 2.8 months to
38 32.4 years. In contrast, surgery data were available for 186 of 187 (99%) of patients with
39 CHD who were alive in December 2013. One hundred forty (75%) of these patients had
40 undergone surgical repair during the study period, a proportion similar to that of the
41 deceased group. The rest ($n=46$) had pending surgeries or anatomical defects that did not
42 require intervention (small ASDs or VSDs, right-sided aortic arch or aberrant subclavian
43 arteries).
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53 As a reference, infant mortality in Chile was approximately 8.0 /1000 live births in the past
54 decade. The fatality rate among hospital discharges for CHD was, on average, 5.4% from
55 2001 to 2011. Eighty-six percent of these deaths occurred in infants one year of age or
56 younger, similar to the observation in the patients with 22q11 deletion. Because the deaths
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in both groups with CHD (general and 22q11DS) were concentrated in the first year of life, we compared case fatality rates for CHD hospital discharges in infants aged 1 year or younger from 2001 to 2011. We found that, on average, fatalities were 3.6-fold higher in infants with 22q11DS compared with the rate reported for CHD nationwide (Table 3).

Because the types of CHD in patients with 22q11DS tend to be more severe than those seen in apparently isolated cases, we compared the fatality rates for specific cardiac defects that are common in the syndrome. We found that in patients with 22q11DS, the fatality rate was 50% among the 22 patients with truncus arteriosus, 32% for the 75 patients with tetralogy of Fallot, 41% for the subgroup of 24 infants with tetralogy of Fallot and pulmonary atresia and 4.2% for the 48 patients with ventricular septal defects (VSDs). In comparison, the average case fatality rates for Chilean patients were 12% for truncus arteriosus, 7% for tetralogy of Fallot and 1.6% for VSDs¹⁰. The latter figures are between 2.6- and 4.6-fold lower than the fatality rates observed for the same structural defects in 22q11DS patients.

Other factors associated with early death were a history of hypocalcemia, measured as total calcium ($p = 0.001$; OR 4.27; 95% CI 1.67-11.15), and airway malacia demonstrated with bronchoscopy ($p = 0.043$; OR 13.375; 95% CI 1.190-110.514). However, information regarding timing of these diagnoses in relationship to surgeries or time of death were unavailable, and the data on airway abnormalities were additionally limited because endoscopic studies were only performed on symptomatic patients. Available information on immune and thyroid function was insufficient for analysis.

Table 1. Causes of death according to the death certificate

	n	%
Cardiac	27	45.8
Cardiac + respiratory failure	9	15.3
Cardiac + infectious	6	10.2
Cardiac + central nervous system anomaly	2	3.4
Cardiac + immunodeficiency	1	1.7
Cardiac + multisystem failure	1	1.7
Infection (pneumonia) or sepsis	7	11.9
Multisystem failure	2	3.4
Respiratory failure	1	1.7
Tracheobronchomalacia	1	1.7
Central nervous system anomaly	1	1.7

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Unknown	1	1.7
TOTAL	59	100.0

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Table 2. Univariate analysis of factors associated with mortality

Characteristic		Deceased, n (%)	Living, n (%)	TOTAL	p value (Fisher's exact test)	OR (95% CI) deceased vs. living patients
		59 (14.1)	360 (85.8)	419		
Gender	Male	26 (44.1)	172 (47.8)	197	0.67	0.87 (0.48-1.58)
	Female	33 (55.9)	188 (52.2)	221		
Cardiac status	CHD data available	52 (14.2)	314 (85.8)	366	<0.0001	5.27 (2.06-13.99)
	With CHD	46 (88.5)	187 (59.5)	233		
	Normal cardiac anatomy	6 (11.5)	127 (40.5)	133		
Calcium status	Calcium data available	24	253	277	0.001	4.27 (1.67-11.15)
	Hypocalcemia	15 (62.5)	71 (28.1)	86		
	Normal calcium	9 (37.5)	182 (71.2)	191		
Airway status	Airway data available	6	246	252	0.0043	13.38 (1.19-110.51)
	Malacia	4 (67)	32 (13)	36		
	Normal airway	2 (33)	214 (87)	216		

Table 3. Case fatality rates for hospital discharges in infants aged 1 year or younger with CHD: a comparison between patients with 22q11DS and the general national data (ICD 10 codes Q20-Q25).

Birth year	Case fatality rates in 22q11DS patients with CHD (per 100 cases)	General case fatality rate for CHD in Chile (per 100 cases) ⁹	Ratio of case fatality for CHD in 22q11DS/general populations
2001	28.57	6.63	4.31
2002	18.18	8.53	2.13
2003	0.00	7.77	0.00
2004	23.81	9.29	2.56
2005	21.43	9.30	2.30
2006	30.00	6.79	4.42
2007	41.67	7.59	5.49
2008	29.41	6.63	4.43
2009	42.11	8.55	4.92
2010	33.33	6.78	4.92
2011	42.86	7.49	5.72
Average	28.31	7.75	3.65

DISCUSSION

Our observations confirm that patients with 22q11DS have high fatality rates. We found that 14.1% of a large cohort of Chilean patients, or 1 in 7, died during the 15-year observation period. For the subgroup of patients with the deletion and CHD, the fatality rate was 19.7% or almost 1 in 5 patients. To our knowledge, this is the largest series to report the case fatality rate and survival for this syndrome.

The majority of deaths occurred during the first year of life and were associated with the presence of CHD, particularly with severe cardiac defects that are common in this syndrome, such as tetralogy Fallot with pulmonary atresia and truncus arteriosus. Right-sided heart failure, which is related to pulmonary vascular resistance, a common complication of these anomalies, has been proposed as an important contributor to mortality^{3,11,12}.

The diagnosis and treatment of CHD has universal coverage under Chilean Health Care Reform¹³, and pediatric cardiac surgeries have been performed in 3 national referral centers since 2005. Therefore, it is unlikely that differences in local clinical practices are the main cause of the high mortality in patients with 22q11DS, at least in the past 8 years. In fact, similar figures have been observed in comparisons of the fatality rates before and after the implementation of universal coverage for CHD diagnosis and treatment, which was guaranteed after the health care reform. Although overall national infant mortality for CHD decreased during this period¹⁰, the impact of universal coverage is less evident for children with severe and complex defects, such as those that are present in patients with 22q11DS. Indeed, we found that patients with 22q11DS had a higher overall fatality rate compared with the national statistics for patients with similar CHDs but without the syndrome; this discrepancy was evident for specific cardiac defects that are common in the syndrome, such as tetralogy of Fallot, truncus arteriosus and VSD. This finding suggests that even for similar anatomic defects, there are additional manifestations and, most likely, other pathophysiologic features in patients with the syndrome that may contribute to higher fatality than is found in cases of apparently isolated defects. Among these features, we found that hypocalcemia and airway abnormalities were also significant risk factors associated with early death. Low calcium levels are common in patients with the deletion, particularly during the cardiac postoperative period. Shen et al.¹¹ determined that the frequency of hypocalcemia and the speed of calcium level decline after surgery is higher in patients with the deletion than in those without and that this difference is

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3 associated with postsurgical complications. The authors did not show an association
4 between hypocalcemia and mortality, as we did in our study, but this difference may be
5 related to their study's smaller sample size (n=19). We did not have parathyroid hormone
6 (PTH) levels for our patients, but other researchers have shown that postoperative
7 hypocalcemia is caused by a decreased PTH reserve^{11,14}. Our results emphasize a need
8 to direct specific attention to the calcium levels of 22q11DS patients during the
9 perioperative period.
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15 Airway malacia was also a risk factor for lethality. This manifestation can be caused by the
16 extrinsic compression by aberrant vessels or by intrinsic airway anomalies in 22q11DS
17 patients¹⁵. Its management often requires prolonged mechanical ventilation, which leads to
18 an increased risk of infection that may also contribute to mortality. Future studies of the
19 pathogenesis, early detection and management strategies of airway anomalies in the
20 syndrome will be relevant for treatment and prognosis.
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26 This study is limited by its retrospective nature, partially complete clinical data (including a
27 lack of accurate information about the timing of certain manifestations, such as
28 hypocalcemia and infections) and biases related to the possible underrecognition of an
29 unknown proportion of patients with the deletion. Nevertheless, in this relatively large
30 series of patients, we found that the presence of 22q11DS adversely affects survival,
31 particularly in individuals with CHD, hypocalcemia and/or airway malacia. There may be a
32 need for modified surgical techniques, timing and/or perioperative management of cardiac
33 and extracardiac manifestations, as proposed by Carotti et al.¹⁶, to improve survival in
34 22q11DS patients and make it at least comparable to their non-syndromic counterparts, as
35 is the current reality for patients with Down syndrome, for example¹⁷.
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53 **Contributions:** GMR and MLG participated in the study concept and design. MLG, MP,
54 GL and PA participated in data acquisition. ID and HL performed the statistical analysis.
55 GMR, GL and CV and PA participated in the drafting and critical revision of the manuscript
56 for important intellectual content. FB and KE provided administrative, technical and
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3 material support. GMR obtained funding and participated in overall study supervision. All of
4 the authors critically reviewed and approved the final version of the manuscript.
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8 **Data sharing:** No additional data are available.
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3 **CASE-FATALITY RATE AND ASSOCIATED FACTORS IN 22Q11 MICRODELETION**
4 **SYNDROME PATIENTS: A RETROSPECTIVE COHORT STUDY**
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Keywords: 22q11 deletion syndrome, congenital heart disease, DiGeorge syndrome, fatality rate, hypocalcemia.

Word count: 2128

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ABSTRACT

Objective: Chromosome 22q11.2 deletion is the most commonly occurring known microdeletion syndrome. Deaths related to the syndrome have been reported, but the magnitude of fatality has not been quantified. This study evaluated the deletion's impact on survival and its clinical manifestations in a large cohort of Chilean patients.

Design: Demographic and clinical data of individuals with FISH- or MLPA-proven 22q11 deletions diagnosed between 1998 and 2013 were collected from medical records and death certificates. Case-fatality rate was calculated and compared with national vital statistics. OR with 95% CI analysis was used to assess the association between clinical manifestations and fatality.

Setting: Genetic services in tertiary care centers in Chile that were following patients with 22q11.2 deletion.

Outcomes: Fatality rate and associated factors

Results: Fifty-nine of 419 patients (14.1%) died during the study period, at a median of 3.4 months and ranging from 0 to 32 years of age. Factors associated with fatality included congenital heart disease (OR 5.27; 95% CI 2.06-13.99; $p < 0.0001$), hypocalcemia (OR 4.27; 95% CI 1.67-11.15; $p < 0.002$) and airway malacia (OR 13.37; 95% CI 1.19-110.51; $p < 0.002$). Patients with deletions and defects such as tetralogy of Fallot with or without pulmonary atresia, truncus arteriosus or ventricular septal defect, had a 2.6- to 4.6-fold higher fatality rate compared with nationwide reports for the same types of defects.

Conclusions: In this cohort, we observed a fatality rate of 14.1%, implying that 1 in 7 patients with 22q11 deletion died during the study period. Significant associations with cardiac defects, hypocalcemia and airway malacia were observed. Furthermore, the fatality risk in patients with 22q11 deletion and cardiac defects exceeded the global figures observed in Chile for infants with structurally similar but apparently isolated anomalies. These observations indicate a need to identify patients who may require specific perioperative management to improve survival.

ARTICLE SUMMARY

Strengths and limitations of the study

- The results are strengthened by the inclusion of a large group of patients with 22q11 deletion, most of whom were followed for over a decade. The sample accounts for the majority of cases in the country, and the participants have had similar access to congenital heart defect diagnosis and repair since 2005 in the context of the National Health Care Reform in Chile.
- The main limitation of our study is that it relied on clinical recognition and confirmation of the deletion; therefore, severe cases with early mortality and undiagnosed cases were not included.
- We recognize that statistical analysis was also limited by partially complete data for some relevant clinical variables, such as calcium levels, airway anatomy and immune function.

INTRODUCTION

Chromosome 22q11 microdeletion syndrome (22q11DS; MIM #188400 and 192430) is the most common known microdeletion syndrome in humans, with an estimated incidence of 1 in 4000 live births¹. It causes congenital heart disease (CHD), hypocalcemia, cognitive disabilities and psychiatric disease, among other symptoms¹. Several authors have reported an increase in post-operative mortality in pediatric patients with CHD and 22q11DS compared with patients with non-syndromic CHD^{2,3}; however, this association appears to be controversial and has not been observed by other authors⁴⁻⁶. In addition, sudden death in adults with 22q11DS has also been described⁷. Given these findings, we sought to investigate survival and factors associated with fatality in a large cohort of Chilean patients with this syndrome.

METHODS

Patients with 22q11DS that was confirmed with FISH (TUPLE 1 Probe, Abbott Molecular, Abbott Park, IL, USA) and/or MLPA (SALSA MLPA P250 DiGeorge probe mix, MRC, Amsterdam, The Netherlands) in one of the 6 clinical cytogenetic laboratories that perform such testing in Chile between 1998 (when FISH testing was clinically introduced in the country) and 2013 were included in the study. The patients were identified at cardiology, cleft palate, genetics or developmental pediatrics clinics; through family support groups;

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3 and/or through periodic surveys to cytogenetics laboratories. Clinical and demographic
4 data were collected from medical records, death certificates when pertinent and/or
5 parental/patient interviews using a standardized questionnaire. Information was gathered
6 retrospectively at the time of inclusion and prospectively thereafter. Living or deceased
7 status in December 2013 was obtained for every participant through the National Civil and
8 Information Registry (www.registrocivil.cl). This longitudinal cohort was recruited as part of
9 consecutive research projects that aim to characterize the syndrome in Chile and identify
10 the clinical, epidemiological and molecular risk factors for the development of individual
11 features of the syndrome. The study was approved by the institutional review boards of the
12 participating centers, and the patients or their parents gave written informed consent.
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20 **Cardiac anatomy was evaluated by a pediatric cardiologist using echocardiogram. Airway**
21 **abnormalities were assessed with bronchoscopy performed by a pediatric pulmonologist,**
22 **and malacia was defined as the collapse of at least 50% of the airway lumen during**
23 **expiration, cough or spontaneous breathing or a < 3:1 ratio of cartilage to membranous**
24 **wall area ⁸.**
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29 The association of demographic features and clinical manifestations with fatality was
30 evaluated using Fisher's exact test and odds ratios. Survival function was estimated using
31 the Kaplan-Meier method. Significant differences in the survival functions of CHD and non-
32 CHD patients were evaluated with the log-rank test. For some clinical features, data were
33 incomplete; therefore, the statistical analysis included only patients with recorded data. As
34 a reference, the results were compared with official case fatality statistics for congenital
35 heart disease (ICD-10, codes Q20-25) from hospital discharges in Chile for 2001-2011, the
36 latter year being the most current nationwide information available at the time of writing ⁹.
37 R software ¹⁰ and SPSS version 20.0 (SPSS Inc., Chicago, IL) were used for statistical
38 analysis. A p value <0.05 was considered statistically significant.
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49 RESULTS

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51 Of 430 known patients with postnatal diagnosis of the deletion, 419 consented to
52 participate in the study. The participants included 198 males (47.2%) and 221 females
53 (52.7%). Seventeen cases (4%) had a parent with the deletion, but this prevalence is a
54 clear underestimate because only those parents with features suggestive of the syndrome
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3 had undergone molecular testing because of insurance coverage limitations. Sixteen of
4 them (94%) were of maternal inheritance.
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7 The median age of inclusion in the cohort was 12 years and ranged from 0 to 52 years.
8 Fifty-nine (14.1%) participants died during the 15-year study period (1998 to 2013). The
9 median age at death was 3.4 months, with a minimum of 3 days and a maximum of 32.4
10 years. Only 2 patients died after 2 years of age: one at 9.9 years from septic shock and
11 one at 32.4 years from pulmonary fibrosis and chronic respiratory insufficiency. Gender
12 was not associated with fatality.
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18 **Table 1 lists the causes of death according to the death certificate.** Cardiac causes were
19 the most common; they were listed as the single cause of death in 27 patients (45.8%) or
20 in combination with other causes in 46 (78%) patients. **Infectious**
21 **causes/immunodeficiency (sepsis, pneumonia, or intra-abdominal source) were the**
22 **second most common cause of death: they were listed as the single primary cause in 7**
23 **patients (11.9%) or in combination with other causes (usually cardiac) in 14 patients**
24 **(23.7%).** The third most common cause of death was related to the respiratory system
25 (respiratory failure, malacia) alone in 2 patients (3.4%) or with other causes in 11 patients
26 (18.6%).
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33 Information about cardiac anatomy was available for 366 patients, corresponding to 87%
34 of the total participants and 88.5% of the deceased. Of the 366 patients for whom cardiac
35 anatomy information was available, 233 (63.7%) had a CHD, and 133 (36.3%) had a
36 structurally normal heart and great vessels according to echocardiogram. The presence of
37 cardiac anomalies was significantly associated with mortality: 46 patients with CHD (19.7%
38 of all patients with CHD) and 6 patients without (4.5% of all patients without CHD) died
39 during the study period (OR 5.27; 95% CI 2.06-13.99; $p < 0.0001$; Table 2). Figure 1
40 compares Kaplan-Meier survival curves for the patients with and without CHD. The 2
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52 **of age (range 11 days to 1.65 years of age). These deaths occurred at a median of 3.6**
53 **months after surgery, ranging from 1 day to 1.2 years.** Those patients with CHD but no
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3 cardiac surgery died earlier, at a median of 0.2 months, ranging from 3 days to 3.7 months
4 of age. The 6 patients without CHD died at a median of 4.7 months, ranging from 2.8
5 months to 32.4 years. In contrast, surgery data were available for 186 of 187 (99%) of
6 patients with CHD who were alive in December 2013. One hundred forty (75%) of these
7 patients had undergone surgical repair during the study period, a proportion similar to that
8 of the deceased group. The rest (n=46) had pending surgeries or anatomical defects that
9 did not require intervention (small ASDs or VSDs, right-sided aortic arch or aberrant
10 subclavian arteries).
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17 As a reference, infant mortality in Chile was approximately 8.0 /1000 live births in the past
18 decade. The fatality rate among hospital discharges for CHD was, on average, 5.4% from
19 2001 to 2011. Eighty-six percent of these deaths occurred in infants one year of age or
20 younger, similar to the observation in the patients with 22q11 deletion. Because the deaths
21 in both groups with CHD (general and 22q11DS) were concentrated in the first year of life,
22 we compared case fatality rates for CHD hospital discharges in infants aged 1 year or
23 younger from 2001 to 2011. We found that, on average, fatalities were 3.6-fold higher in
24 infants with 22q11DS compared with the rate reported for CHD nationwide (Table 3).
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31 Because the types of CHD in patients with 22q11DS tend to be more severe than those
32 seen in apparently isolated cases, we compared the fatality rates for specific cardiac
33 defects that are common in the syndrome. We found that in patients with 22q11DS, the
34 fatality rate was 50% among the 22 patients with truncus arteriosus, 32% for the 75
35 patients with tetralogy of Fallot, 41% for the subgroup of 24 infants with tetralogy of Fallot
36 and pulmonary atresia and 4.2% for the 48 patients with ventricular septal defects (VSDs).
37 In comparison, the average case fatality rates for Chilean patients were 12% for truncus
38 arteriosus, 7% for tetralogy of Fallot and 1.6% for VSDs¹⁰. The latter figures are between
39 2.6- and 4.6-fold lower than the fatality rates observed for the same structural defects in
40 22q11DS patients.
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48 Other factors associated with early death were a history of hypocalcemia, measured as
49 total calcium (p =0.001; OR 4.27; 95% CI 1.67-11.15), and airway malacia demonstrated
50 with bronchoscopy (p= 0.043; OR 13.375; 95% CI 1.190-110.514). However, information
51 regarding timing of these diagnoses in relationship to surgeries or time of death were
52 unavailable, and the data on airway abnormalities were additionally limited because
53 endoscopic studies were only performed on symptomatic patients. Available information on
54 immune and thyroid function was insufficient for analysis.
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Table 1. Causes of death according to the death certificate

	n	%
Cardiac	27	45.8
Cardiac + respiratory failure	9	15.3
Cardiac + infectious	6	10.2
Cardiac + central nervous system anomaly	2	3.4
Cardiac + immunodeficiency	1	1.7
Cardiac + multisystem failure	1	1.7
Infection (pneumonia) or sepsis	7	11.9
Multisystem failure	2	3.4
Respiratory failure	1	1.7
Tracheobronchomalacia	1	1.7
Central nervous system anomaly	1	1.7
Unknown	1	1.7
TOTAL	59	100.0

Table 2. Univariate analysis of factors associated with mortality

Characteristic		Deceased, n (%)	Living, n (%)	TOTAL	p value (Fisher's exact test)	OR (95% CI) deceased vs. living patients
		59 (14.1)	360 (85.8)	419		
Gender	Male	26 (44.1)	172 (47.8)	197	0.67	0.87 (0.48-1.58)
	Female	33 (55.9)	188 (52.2)	221		
Cardiac status	CHD data available	52 (14.2)	314 (85.8)	366	<0.0001	5.27 (2.06-13.99)
	With CHD	46 (88.5)	187 (59.5)	233		
	Normal cardiac anatomy	6 (11.5)	127 (40.5)	133		
Calcium status	Calcium data available	24	253	277	0.001	4.27 (1.67-11.15)
	Hypocalcemia	15 (62.5)	71 (28.1)	86		
	Normal calcium	9 (37.5)	182 (71.2)	191		
Airway status	Airway data available	6	246	252	0.0043	13.38 (1.19-110.51)
	Malacia	4 (67)	32 (13)	36		
	Normal airway	2 (33)	214 (87)	216		

Table 3. Case fatality rates for hospital discharges in infants aged 1 year or younger with CHD: a comparison between patients with 22q11DS and the general national data (ICD 10 codes Q20-Q25).

Birth year	Case fatality rates in 22q11DS patients with CHD (per 100 cases)	General case fatality rate for CHD in Chile (per 100 cases) ⁹	Ratio of case fatality for CHD in 22q11DS/general populations
2001	28.57	6.63	4.31
2002	18.18	8.53	2.13
2003	0.00	7.77	0.00
2004	23.81	9.29	2.56
2005	21.43	9.30	2.30
2006	30.00	6.79	4.42
2007	41.67	7.59	5.49
2008	29.41	6.63	4.43
2009	42.11	8.55	4.92
2010	33.33	6.78	4.92
2011	42.86	7.49	5.72
Average	28.31	7.75	3.65

DISCUSSION

Our observations confirm that patients with 22q11DS have high fatality rates. We found that 14.1% of a large cohort of Chilean patients, or 1 in 7, died during the 15-year observation period. For the subgroup of patients with the deletion and CHD, the fatality rate was 19.7% or almost 1 in 5 patients. To our knowledge, this is the largest series to report the case fatality rate and survival for this syndrome.

The majority of deaths occurred during the first year of life and were associated with the presence of CHD, particularly with severe cardiac defects that are common in this syndrome, such as tetralogy Fallot with pulmonary atresia and truncus arteriosus. Right-sided heart failure, which is related to pulmonary vascular resistance, a common complication of these anomalies, has been proposed as an important contributor to mortality^{3,11,12}.

The diagnosis and treatment of CHD has universal coverage under Chilean Health Care Reform¹³, and pediatric cardiac surgeries have been performed in 3 national referral centers since 2005. Therefore, it is unlikely that differences in local clinical practices are the main cause of the high mortality in patients with 22q11DS, at least in the past 8 years. In fact, similar figures have been observed in comparisons of the fatality rates before and after the implementation of universal coverage for CHD diagnosis and treatment, which was guaranteed after the health care reform. Although overall national infant mortality for CHD decreased during this period¹⁰, the impact of universal coverage is less evident for children with severe and complex defects, such as those that are present in patients with 22q11DS. Indeed, we found that patients with 22q11DS had a higher overall fatality rate compared with the national statistics for patients with similar CHDs but without the syndrome; this discrepancy was evident for specific cardiac defects that are common in the syndrome, such as tetralogy of Fallot, truncus arteriosus and VSD. This finding suggests that even for similar anatomic defects, there are additional manifestations and, most likely, other pathophysiologic features in patients with the syndrome that may contribute to higher fatality than is found in cases of apparently isolated defects. Among these features, we found that hypocalcemia and airway abnormalities were also significant risk factors associated with early death. Low calcium levels are common in patients with the deletion, particularly during the cardiac postoperative period. Shen et al.¹¹ determined that the frequency of hypocalcemia and the speed of calcium level decline after surgery is higher in patients with the deletion than in those without and that this difference is

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3 associated with postsurgical complications. The authors did not show an association
4 between hypocalcemia and mortality, as we did in our study, but this difference may be
5 related to their study's smaller sample size (n=19). We did not have parathyroid hormone
6 (PTH) levels for our patients, but other researchers have shown that postoperative
7 hypocalcemia is caused by a decreased PTH reserve^{11,14}. Our results emphasize a need
8 to direct specific attention to the calcium levels of 22q11DS patients during the
9 perioperative period.
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15 Airway malacia was also a risk factor for lethality. This manifestation can be caused by the
16 extrinsic compression by aberrant vessels or by intrinsic airway anomalies in 22q11DS
17 patients¹⁵. Its management often requires prolonged mechanical ventilation, which leads to
18 an increased risk of infection that may also contribute to mortality. Future studies of the
19 pathogenesis, early detection and management strategies of airway anomalies in the
20 syndrome will be relevant for treatment and prognosis.
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26 This study is limited by its retrospective nature, partially complete clinical data (including a
27 lack of accurate information about the timing of certain manifestations, such as
28 hypocalcemia and infections) and biases related to the possible underrecognition of an
29 unknown proportion of patients with the deletion. Nevertheless, in this relatively large
30 series of patients, we found that the presence of 22q11DS adversely affects survival,
31 particularly in individuals with CHD, hypocalcemia and/or airway malacia. There may be a
32 need for modified surgical techniques, timing and/or perioperative management of cardiac
33 and extracardiac manifestations, as proposed by Carotti et al.¹⁶, to improve survival in
34 22q11DS patients and make it at least comparable to their non-syndromic counterparts, as
35 is the current reality for patients with Down syndrome, for example¹⁷.
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49

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53 **Contributions:** GMR and MLG participated in the study concept and design. MLG, MP,
54 GL and PA participated in data acquisition. ID and HL performed the statistical analysis.
55 GMR, GL and CV and PA participated in the drafting and critical revision of the manuscript
56 for important intellectual content. FB and KE provided administrative, technical and
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material support. GMR obtained funding and participated in overall study supervision. All of the authors critically reviewed and approved the final version of the manuscript.

Data sharing: No additional data are available.

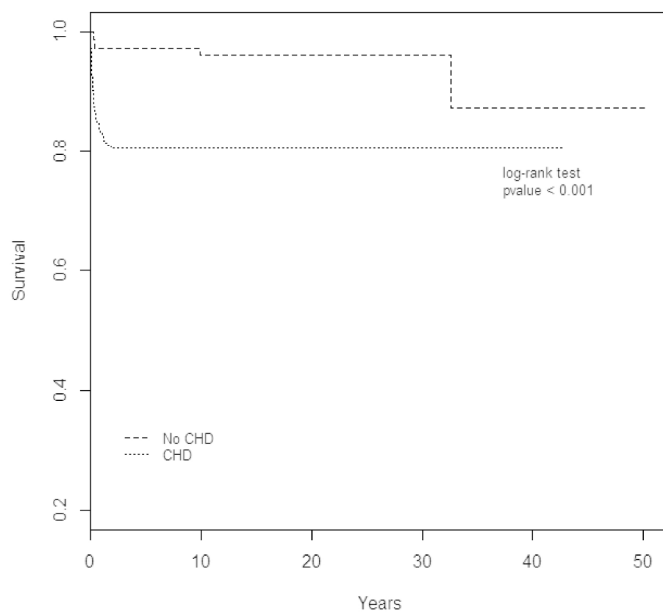
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Figure 1. Kaplan-Meier survival curves for 22q11DS patients with or without CHD



n, no CHD	133	91	31	15	7	1
n CHD	233	104	28	4	1	0
TOTAL	366	195	59	19	8	1

215x279mm (300 x 300 DPI)

BMJ Open

CASE-FATALITY RATE AND ASSOCIATED FACTORS IN 22Q11 MICRODELETION SYNDROME PATIENTS: A RETROSPECTIVE COHORT STUDY

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3 **CASE-FATALITY RATE AND ASSOCIATED FACTORS IN 22Q11 MICRODELETION**
4 **SYNDROME PATIENTS: A RETROSPECTIVE COHORT STUDY**
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ABSTRACT

Objective: Chromosome 22q11.2 deletion is the most commonly occurring known microdeletion syndrome. Deaths related to the syndrome have been reported, but the magnitude of fatality has not been quantified. This study evaluated the deletion's impact on survival and its clinical manifestations in a large cohort of Chilean patients.

Design: Demographic and clinical data of individuals with FISH- or MLPA-proven 22q11 deletions diagnosed between 1998 and 2013 were collected from medical records and death certificates. Case-fatality rate was calculated and compared with national vital statistics. OR with 95% CI analysis was used to assess the association between clinical manifestations and fatality.

Setting: Genetic services in tertiary care centers in Chile that were following patients with 22q11.2 deletion.

Outcomes: Fatality rate and associated factors

Results: Fifty-nine of 419 patients (14.1%) died during the study period, at a median of 3.4 months and ranging from 0 to 32 years of age. Factors associated with fatality included congenital heart disease (OR 5.27; 95% CI 2.06-13.99; $p < 0.0001$), hypocalcemia (OR 4.27; 95% CI 1.67-11.15; $p < 0.002$) and airway malacia (OR 13.37; 95% CI 1.19-110.51; $p < 0.002$). Patients with deletions and defects such as tetralogy of Fallot with or without pulmonary atresia, truncus arteriosus or ventricular septal defect, had a 2.6- to 4.6-fold higher fatality rate compared with nationwide reports for the same types of defects.

Conclusions: In this cohort, we observed a fatality rate of 14.1%, implying that 1 in 7 patients with 22q11 deletion died during the study period. Significant associations with cardiac defects, hypocalcemia and airway malacia were observed. Furthermore, the fatality risk in patients with 22q11 deletion and cardiac defects exceeded the global figures observed in Chile for infants with structurally similar but apparently isolated anomalies. These observations indicate a need to identify patients who may require specific perioperative management to improve survival.

ARTICLE SUMMARY

Strengths and limitations of the study

- The results are strengthened by the inclusion of a large group of patients with 22q11 deletion, most of whom were followed for over a decade. The sample accounts for the majority of cases in the country, and the participants have had similar access to congenital heart defect diagnosis and repair since 2005 in the context of the National Health Care Reform in Chile.
- The main limitation of our study is that it relied on clinical recognition and confirmation of the deletion; therefore, severe cases with early mortality and undiagnosed cases were not included.
- We recognize that statistical analysis is also limited by partially complete data for some relevant clinical variables, such as calcium levels, airway anatomy, immune function and specific mode of death.

INTRODUCTION

Chromosome 22q11 microdeletion syndrome (22q11DS; MIM #188400 and 192430) is the most common known microdeletion syndrome in humans, with an estimated incidence of 1 in 4000 live births¹. It causes congenital heart disease (CHD), hypocalcemia, cognitive disabilities and psychiatric disease, among other symptoms¹. Several authors have reported an increase in post-operative mortality in pediatric patients with CHD and 22q11DS compared with patients with non-syndromic CHD^{2,3}; however, this association appears to be controversial and has not been observed by other authors⁴⁻⁶. In addition, sudden death in adults with 22q11DS has also been described⁷. Given these findings, we sought to investigate survival and factors associated with fatality in a large cohort of Chilean patients with this syndrome.

METHODS

Patients with 22q11DS that was confirmed with FISH (TUPLE 1 Probe, Abbott Molecular, Abbott Park, IL, USA) and/or MLPA (SALSA MLPA P250 DiGeorge probe mix, MRC, Amsterdam, The Netherlands) in one of the 6 clinical cytogenetic laboratories that perform such testing in Chile between 1998 (when FISH testing was clinically introduced in the country) and 2013 were included in the study. The patients were identified at cardiology, cleft palate, genetics or developmental pediatrics clinics; through family support groups;

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3 and/or through periodic surveys to cytogenetics laboratories. Clinical and demographic
4 data were collected from medical records, death certificates when pertinent and/or
5 parental/patient interviews using a standardized questionnaire. Information was gathered
6 retrospectively at the time of inclusion and prospectively thereafter. Living or deceased
7 status in December 2013 was obtained for every participant through the National Civil and
8 Information Registry (www.registrocivil.cl). This longitudinal cohort was recruited as part of
9 consecutive research projects that aim to characterize the syndrome in Chile and identify
10 the clinical, epidemiological and molecular risk factors for the development of individual
11 features of the syndrome. The study was approved by the institutional review boards of the
12 participating centers, and the patients or their parents gave written informed consent.
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20 Cardiac anatomy was evaluated by a pediatric cardiologist using echocardiogram. Airway
21 abnormalities were assessed with bronchoscopy performed by a pediatric pulmonologist,
22 and malacia was defined as the collapse of at least 50% of the airway lumen during
23 expiration, cough or spontaneous breathing or a < 3:1 ratio of cartilage to membranous
24 wall area ⁸.
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29 The association of demographic features and clinical manifestations with fatality was
30 evaluated using Fisher's exact test and odds ratios. Survival function was estimated using
31 the Kaplan-Meier method. Significant differences in the survival functions of CHD and non-
32 CHD patients were evaluated with the log-rank test. For some clinical features, data were
33 incomplete; therefore, the statistical analysis included only patients with recorded data. As
34 a reference, the results were compared with official case fatality statistics for congenital
35 heart disease (ICD-10, codes Q20-25) from hospital discharges in Chile for 2001-2011, the
36 latter year being the most current nationwide information available at the time of writing ⁹.
37 R software ¹⁰ and SPSS version 20.0 (SPSS Inc., Chicago, IL) were used for statistical
38 analysis. A p value <0.05 was considered statistically significant.
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49 RESULTS

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51 Of 430 known patients with postnatal diagnosis of the deletion, 419 consented to
52 participate in the study. The participants included 198 males (47.2%) and 221 females
53 (52.7%). Seventeen cases (4%) had a parent with the deletion, but this prevalence is a
54 clear underestimate because only those parents with features suggestive of the syndrome
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3 had undergone molecular testing because of insurance coverage limitations. Sixteen of
4 them (94%) were of maternal inheritance.
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7 The median age of inclusion in the cohort was 12 years and ranged from 0 to 52 years.
8 Fifty-nine (14.1%) participants died during the 15-year study period (1998 to 2013). The
9 median age at death was 3.4 months, with a minimum of 3 days and a maximum of 32.4
10 years. Only 2 patients died after 2 years of age: one at 9.9 years from septic shock and
11 one at 32.4 years from pulmonary fibrosis and chronic respiratory insufficiency. Gender
12 was not associated with fatality.
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17 Table 1 lists the causes of death according to the death certificate. Cardiac causes were
18 the most common; they were listed as the single cause of death in 27 patients (45.8%) or
19 in combination with other causes in 46 (78%) patients. Infectious
20 causes/immunodeficiency (sepsis, pneumonia, or intra-abdominal source) were the
21 second most common cause of death: they were listed as the single primary cause in 7
22 patients (11.9%) or in combination with other causes (usually cardiac) in 14 patients
23 (23.7%). The third most common cause of death was related to the respiratory system
24 (respiratory failure, malacia) alone in 2 patients (3.4%) or with other causes in 11 patients
25 (18.6%). Information on the mode of death was unavailable for most patients because this
26 is not listed in death certificates.
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35 Information about cardiac anatomy was available for 366 patients, corresponding to 87%
36 of the total participants and 88.5% of the deceased. Of the 366 patients for whom cardiac
37 anatomy information was available, 233 (63.7%) had a CHD, and 133 (36.3%) had a
38 structurally normal heart and great vessels according to echocardiogram. The presence of
39 cardiac anomalies was significantly associated with mortality: 46 patients with CHD (19.7%
40 of all patients with CHD) and 6 patients without (4.5% of all patients without CHD) died
41 during the study period (OR 5.27; 95% CI 2.06-13.99; $p < 0.0001$; Table 2). Figure 1
42 compares Kaplan-Meier survival curves for the patients with and without CHD. The 2
43 patients who died after 2 years of age did not have CHD.
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50 Information regarding cardiac surgery was available for 40 of the 46 deceased patients
51 with known CHD (87%). Of the 40 deceased patients with surgical information, 10 (25%)
52 died before operative repair, 3 (7.5%) died during surgery, and 27 (67.5%) died after
53 surgery. Patients with CHD who underwent surgical repair died at a median of 3.5 months
54 of age (range 11 days to 1.65 years of age). These deaths occurred at a median of 3.6
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3 months after surgery, ranging from 1 day to 1.2 years. Those with CHD but no cardiac
4 surgery died earlier, at a median of 0.2 months, ranging from 3 days to 3.7 months of age.
5 The 6 patients without CHD died at a median of 4.7 months, ranging from 2.8 months to
6 32.4 years. In contrast, surgery data were available for 186 of 187 (99%) of patients with
7 CHD who were alive in December 2013. One hundred forty (75%) of these patients had
8 undergone surgical repair during the study period, a proportion similar to that of the
9 deceased group. The rest (n=46) had pending surgeries or anatomical defects that did not
10 require intervention (small ASDs or VSDs, right-sided aortic arch or aberrant subclavian
11 arteries).

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19 As a reference, infant mortality in Chile was approximately 8.0 /1000 live births in the past
20 decade. The fatality rate among hospital discharges for CHD was, on average, 5.4% from
21 2001 to 2011. Eighty-six percent of these deaths occurred in infants one year of age or
22 younger, similar to the observation in the patients with 22q11 deletion. Because the deaths
23 in both groups with CHD (general and 22q11DS) were concentrated in the first year of life,
24 we compared case fatality rates for CHD hospital discharges in infants aged 1 year or
25 younger from 2001 to 2011. We found that, on average, fatalities were 3.6-fold higher in
26 infants with 22q11DS compared with the rate reported for CHD nationwide (Table 3).

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33 The types of CHD in patients with 22q11DS tend to be more severe than those seen in
34 apparently isolated cases, thus we compared the fatality rates for specific cardiac defects
35 that are common in the syndrome. We found that in patients with 22q11DS, the case-
36 fatality rate was 50% among the 22 patients with truncus arteriosus, 32% for the 75
37 patients with tetralogy of Fallot, 41% for the subgroup of 24 infants with tetralogy of Fallot
38 and pulmonary atresia and 4.2% for the 48 patients with ventricular septal defects (VSDs).
39 In comparison, the case fatality rates for Chilean patients were 12% for truncus arteriosus,
40 7% for tetralogy of Fallot and 1.6% for VSDs¹⁰. The latter figures are between 2.6- and
41 4.6-fold lower than the fatality rates observed for the same structural defects in 22q11DS
42 patients.

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50 Other factors associated with early death were a history of hypocalcemia, measured as
51 total calcium ($p=0.001$; OR 4.27; 95% CI 1.67-11.15), and airway malacia demonstrated
52 with bronchoscopy ($p=0.043$; OR 13.375; 95% CI 1.190-110.514). However, information
53 regarding timing of these diagnoses in relationship to surgeries or time of death were
54 unavailable, and the data on airway abnormalities were additionally limited because
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endoscopic studies were only performed on symptomatic patients. Available information on immune and thyroid function was insufficient for analysis.

Table 1. Causes of death according to the death certificate

	n	%
Cardiac	27	45.8
Cardiac + respiratory failure	9	15.3
Cardiac + infectious	6	10.2
Cardiac + central nervous system anomaly	2	3.4
Cardiac + immunodeficiency	1	1.7
Cardiac + multisystem failure	1	1.7
Infection (pneumonia) or sepsis	7	11.9
Multisystem failure	2	3.4
Respiratory failure	1	1.7
Tracheobronchomalacia	1	1.7
Central nervous system anomaly	1	1.7
Unknown	1	1.7
TOTAL	59	100.0

Table 2. Univariate analysis of factors associated with mortality

Characteristic		Deceased, n (%)	Living, n (%)	TOTAL	p value (Fisher's exact test)	OR (95% CI) deceased vs. living patients
		59 (14.1)	360 (85.8)	419		
Gender	Male	26 (44.1)	172 (47.8)	198	0.67	0.87 (0.48-1.58)
	Female	33 (55.9)	188 (52.2)	221		
Cardiac status	CHD data available	52 (14.2)	314 (85.8)	366	<0.0001	5.27 (2.06-13.99)
	With CHD	46 (88.5)	187 (59.5)	233		
	Normal cardiac anatomy	6 (11.5)	127 (40.5)	133		
Calcium status	Calcium data available	24	253	277	0.001	4.27 (1.67-11.15)
	Hypocalcemia	15 (62.5)	71 (28.1)	86		
	Normal calcium	9 (37.5)	182 (71.2)	191		
Airway status	Airway data available	6	246	252	0.0043	13.38 (1.19-110.51)
	Malacia	4 (67)	32 (13)	36		
	Normal airway	2 (33)	214 (87)	216		

Table 3. Case fatality rates for hospital discharges in infants aged 1 year or younger with CHD: a comparison between patients with 22q11DS and the general national data (ICD 10 codes Q20-Q25).

Birth year	Case fatality rates in 22q11DS patients with CHD (per 100 cases)	General case fatality rate for CHD in Chile (per 100 cases)⁹	Ratio of case fatality for CHD in 22q11DS/general populations
2001	28.57	6.63	4.31
2002	18.18	8.53	2.13
2003	0.00	7.77	0.00
2004	23.81	9.29	2.56
2005	21.43	9.30	2.30
2006	30.00	6.79	4.42
2007	41.67	7.59	5.49
2008	29.41	6.63	4.43
2009	42.11	8.55	4.92
2010	33.33	6.78	4.92
2011	42.86	7.49	5.72
Average	28.31	7.75	3.65

DISCUSSION

Our observations confirm that patients with 22q11DS have high fatality rates. We found that 14.1% of a large cohort of Chilean patients, or 1 in 7, died during the 15-year observation period. For the subgroup of patients with the deletion and CHD, the fatality rate was 19.7% or almost 1 in 5 patients. To our knowledge, this is the largest series to report the case fatality rate and survival for this syndrome.

The majority of deaths occurred during the first year of life and were associated with the presence of CHD, particularly with severe cardiac defects that are common in this syndrome, such as tetralogy Fallot with pulmonary atresia and truncus arteriosus. Right-sided heart failure, which is related to pulmonary vascular resistance, a common complication of these anomalies, has been proposed as an important contributor to mortality^{3,11,12}.

The diagnosis and treatment of CHD has universal coverage under Chilean Health Care Reform¹³, and pediatric cardiac surgeries have been performed in 3 national referral centers since 2005. Therefore, it is unlikely that differences in local clinical practices are the main cause of the high mortality in patients with 22q11DS, at least in the past 8 years. In fact, similar figures have been observed in comparisons of the fatality rates before and after the implementation of universal coverage for CHD diagnosis and treatment, which was guaranteed after the health care reform. Although overall national infant mortality for CHD decreased during this period¹⁰, the impact of universal coverage is less evident for children with severe and complex defects, such as those that are present in patients with 22q11DS. Indeed, we found that patients with 22q11DS had a higher overall fatality rate compared with the national statistics for patients with similar CHDs but without the syndrome; this discrepancy was evident for specific cardiac defects that are common in the syndrome, such as tetralogy of Fallot, truncus arteriosus and VSD. This finding suggests that even for similar anatomic defects, there are additional manifestations and, most likely, other pathophysiologic features in patients with the syndrome that may contribute to higher fatality than is found in cases of apparently isolated defects. Among these features, we found that hypocalcemia and airway abnormalities were also significant risk factors associated with early death. Low calcium levels are common in patients with the deletion, particularly during the cardiac postoperative period. Shen et al.¹¹ determined that the frequency of hypocalcemia and the speed of calcium level decline after surgery is higher in patients with the deletion than in those without and that this difference is

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3 associated with postsurgical complications. The authors did not show an association
4 between hypocalcemia and mortality, as we did in our study, but this difference may be
5 related to their study's smaller sample size (n=19). We did not have parathyroid hormone
6 (PTH) levels for our patients, but other researchers have shown that postoperative
7 hypocalcemia is caused by a decreased PTH reserve^{11,14}. Our results emphasize a need
8 to direct specific attention to the calcium levels of 22q11DS patients during the
9 perioperative period.
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15 Airway malacia was also a risk factor for lethality. This manifestation can be caused by the
16 extrinsic compression by aberrant vessels or by intrinsic airway anomalies in 22q11DS
17 patients¹⁵. Its management often requires prolonged mechanical ventilation, which leads to
18 an increased risk of infection that may also contribute to mortality. Future studies of the
19 pathogenesis, early detection and management strategies of airway anomalies in the
20 syndrome will be relevant for treatment and prognosis.
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26 This study is limited by its retrospective nature, partially complete clinical data, including a
27 lack of accurate information about the timing of certain manifestations, such as
28 hypocalcemia, infections and mode of death, and biases related to the possible
29 underrecognition of an unknown proportion of patients with the deletion. Nevertheless, in
30 this relatively large series of patients, we found that the presence of 22q11DS adversely
31 affects survival, particularly in individuals with CHD, hypocalcemia and/or airway malacia.
32 There may be a need for modified surgical techniques, timing and/or perioperative
33 management of cardiac and extracardiac manifestations, as proposed by Carotti et al.¹⁶,
34 to improve survival in 22q11DS patients and make it at least comparable to their non-
35 syndromic counterparts, as is the current reality for patients with Down syndrome, for
36 example¹⁷.
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56 **Contributions:** GMR and MLG participated in the study concept and design. MLG, MP,
57 GL and PA participated in data acquisition. ID and HL performed the statistical analysis.
58 GMR, GL and CV and PA participated in the drafting and critical revision of the manuscript
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4 material support. GMR obtained funding and participated in overall study supervision. All of
5 the authors critically reviewed and approved the final version of the manuscript.
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10 **Data sharing:** No additional data are available.
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3 **CASE-FATALITY RATE AND ASSOCIATED FACTORS IN 22Q11 MICRODELETION**
4 **SYNDROME PATIENTS: A RETROSPECTIVE COHORT STUDY**
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4 fatality rate, hypocalcemia.
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For peer review only

ABSTRACT

Objective: Chromosome 22q11.2 deletion is the most commonly occurring known microdeletion syndrome. Deaths related to the syndrome have been reported, but the magnitude of fatality has not been quantified. This study evaluated the deletion's impact on survival and its clinical manifestations in a large cohort of Chilean patients.

Design: Demographic and clinical data of individuals with FISH- or MLPA-proven 22q11 deletions diagnosed between 1998 and 2013 were collected from medical records and death certificates. Case-fatality rate was calculated and compared with national vital statistics. OR with 95% CI analysis was used to assess the association between clinical manifestations and fatality.

Setting: Genetic services in tertiary care centers in Chile that were following patients with 22q11.2 deletion.

Outcomes: Fatality rate and associated factors

Results: Fifty-nine of 419 patients (14.1%) died during the study period, at a median of 3.4 months and ranging from 0 to 32 years of age. Factors associated with fatality included congenital heart disease (OR 5.27; 95% CI 2.06-13.99; $p < 0.0001$), hypocalcemia (OR 4.27; 95% CI 1.67-11.15; $p < 0.002$) and airway malacia (OR 13.37; 95% CI 1.19-110.51; $p < 0.002$). Patients with deletions and defects such as tetralogy of Fallot with or without pulmonary atresia, truncus arteriosus or ventricular septal defect, had a 2.6- to 4.6-fold higher fatality rate compared with nationwide reports for the same types of defects.

Conclusions: In this cohort, we observed a fatality rate of 14.1%, implying that 1 in 7 patients with 22q11 deletion died during the study period. Significant associations with cardiac defects, hypocalcemia and airway malacia were observed. Furthermore, the fatality risk in patients with 22q11 deletion and cardiac defects exceeded the global figures observed in Chile for infants with structurally similar but apparently isolated anomalies. These observations indicate a need to identify patients who may require specific perioperative management to improve survival.

ARTICLE SUMMARY

Strengths and limitations of the study

- The results are strengthened by the inclusion of a large group of patients with 22q11 deletion, most of whom were followed for over a decade. The sample accounts for the majority of cases in the country, and the participants have had similar access to congenital heart defect diagnosis and repair since 2005 in the context of the National Health Care Reform in Chile.
- The main limitation of our study is that it relied on clinical recognition and confirmation of the deletion; therefore, severe cases with early mortality and undiagnosed cases were not included.
- We recognize that statistical analysis is also limited by partially complete data for some relevant clinical variables, such as calcium levels, airway anatomy, immune function and specific mode of death.

INTRODUCTION

Chromosome 22q11 microdeletion syndrome (22q11DS; MIM #188400 and 192430) is the most common known microdeletion syndrome in humans, with an estimated incidence of 1 in 4000 live births¹. It causes congenital heart disease (CHD), hypocalcemia, cognitive disabilities and psychiatric disease, among other symptoms¹. Several authors have reported an increase in post-operative mortality in pediatric patients with CHD and 22q11DS compared with patients with non-syndromic CHD^{2,3}; however, this association appears to be controversial and has not been observed by other authors⁴⁻⁶. In addition, sudden death in adults with 22q11DS has also been described⁷. Given these findings, we sought to investigate survival and factors associated with fatality in a large cohort of Chilean patients with this syndrome.

METHODS

Patients with 22q11DS that was confirmed with FISH (TUPLE 1 Probe, Abbott Molecular, Abbott Park, IL, USA) and/or MLPA (SALSA MLPA P250 DiGeorge probe mix, MRC, Amsterdam, The Netherlands) in one of the 6 clinical cytogenetic laboratories that perform such testing in Chile between 1998 (when FISH testing was clinically introduced in the country) and 2013 were included in the study. The patients were identified at cardiology, cleft palate, genetics or developmental pediatrics clinics; through family support groups;

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3 and/or through periodic surveys to cytogenetics laboratories. Clinical and demographic
4 data were collected from medical records, death certificates when pertinent and/or
5 parental/patient interviews using a standardized questionnaire. Information was gathered
6 retrospectively at the time of inclusion and prospectively thereafter. Living or deceased
7 status in December 2013 was obtained for every participant through the National Civil and
8 Information Registry (www.registrocivil.cl). This longitudinal cohort was recruited as part of
9 consecutive research projects that aim to characterize the syndrome in Chile and identify
10 the clinical, epidemiological and molecular risk factors for the development of individual
11 features of the syndrome. The study was approved by the institutional review boards of the
12 participating centers, and the patients or their parents gave written informed consent.
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20 Cardiac anatomy was evaluated by a pediatric cardiologist using echocardiogram. Airway
21 abnormalities were assessed with bronchoscopy performed by a pediatric pulmonologist,
22 and malacia was defined as the collapse of at least 50% of the airway lumen during
23 expiration, cough or spontaneous breathing or a < 3:1 ratio of cartilage to membranous
24 wall area ⁸.
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29 The association of demographic features and clinical manifestations with fatality was
30 evaluated using Fisher's exact test and odds ratios. Survival function was estimated using
31 the Kaplan-Meier method. Significant differences in the survival functions of CHD and non-
32 CHD patients were evaluated with the log-rank test. For some clinical features, data were
33 incomplete; therefore, the statistical analysis included only patients with recorded data. As
34 a reference, the results were compared with official case fatality statistics for congenital
35 heart disease (ICD-10, codes Q20-25) from hospital discharges in Chile for 2001-2011, the
36 latter year being the most current nationwide information available at the time of writing ⁹.
37 R software ¹⁰ and SPSS version 20.0 (SPSS Inc., Chicago, IL) were used for statistical
38 analysis. A p value <0.05 was considered statistically significant.
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49 RESULTS

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51 Of 430 known patients with postnatal diagnosis of the deletion, 419 consented to
52 participate in the study. The participants included 198 males (47.2%) and 221 females
53 (52.7%). Seventeen cases (4%) had a parent with the deletion, but this prevalence is a
54 clear underestimate because only those parents with features suggestive of the syndrome
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3 had undergone molecular testing because of insurance coverage limitations. Sixteen of
4 them (94%) were of maternal inheritance.
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7 The median age of inclusion in the cohort was 12 years and ranged from 0 to 52 years.
8 Fifty-nine (14.1%) participants died during the 15-year study period (1998 to 2013). The
9 median age at death was 3.4 months, with a minimum of 3 days and a maximum of 32.4
10 years. Only 2 patients died after 2 years of age: one at 9.9 years from septic shock and
11 one at 32.4 years from pulmonary fibrosis and chronic respiratory insufficiency. Gender
12 was not associated with fatality.
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17 Table 1 lists the causes of death according to the death certificate. Cardiac causes were
18 the most common; they were listed as the single cause of death in 27 patients (45.8%) or
19 in combination with other causes in 46 (78%) patients. Infectious
20 causes/immunodeficiency (sepsis, pneumonia, or intra-abdominal source) were the
21 second most common cause of death: they were listed as the single primary cause in 7
22 patients (11.9%) or in combination with other causes (usually cardiac) in 14 patients
23 (23.7%). The third most common cause of death was related to the respiratory system
24 (respiratory failure, malacia) alone in 2 patients (3.4%) or with other causes in 11 patients
25 (18.6%). Information on the mode of death was unavailable for most patients because this
26 is not listed in death certificates.
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35 Information about cardiac anatomy was available for 366 patients, corresponding to 87%
36 of the total participants and 88.5% of the deceased. Of the 366 patients for whom cardiac
37 anatomy information was available, 233 (63.7%) had a CHD, and 133 (36.3%) had a
38 structurally normal heart and great vessels according to echocardiogram. The presence of
39 cardiac anomalies was significantly associated with mortality: 46 patients with CHD (19.7%
40 of all patients with CHD) and 6 patients without (4.5% of all patients without CHD) died
41 during the study period (OR 5.27; 95% CI 2.06-13.99; $p < 0.0001$; Table 2). Figure 1
42 compares Kaplan-Meier survival curves for the patients with and without CHD. The 2
43 patients who died after 2 years of age did not have CHD.
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50 Information regarding cardiac surgery was available for 40 of the 46 deceased patients
51 with known CHD (87%). Of the 40 deceased patients with surgical information, 10 (25%)
52 died before operative repair, 3 (7.5%) died during surgery, and 27 (67.5%) died after
53 surgery. Patients with CHD who underwent surgical repair died at a median of 3.5 months
54 of age (range 11 days to 1.65 years of age). These deaths occurred at a median of 3.6
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3 months after surgery, ranging from 1 day to 1.2 years. Those with CHD but no cardiac
4 surgery died earlier, at a median of 0.2 months, ranging from 3 days to 3.7 months of age.
5 The 6 patients without CHD died at a median of 4.7 months, ranging from 2.8 months to
6 32.4 years. In contrast, surgery data were available for 186 of 187 (99%) of patients with
7 CHD who were alive in December 2013. One hundred forty (75%) of these patients had
8 undergone surgical repair during the study period, a proportion similar to that of the
9 deceased group. The rest (n=46) had pending surgeries or anatomical defects that did not
10 require intervention (small ASDs or VSDs, right-sided aortic arch or aberrant subclavian
11 arteries).

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13 As a reference, infant mortality in Chile was approximately 8.0 /1000 live births in the past
14 decade. The fatality rate among hospital discharges for CHD was, on average, 5.4% from
15 2001 to 2011. Eighty-six percent of these deaths occurred in infants one year of age or
16 younger, similar to the observation in the patients with 22q11 deletion. Because the deaths
17 in both groups with CHD (general and 22q11DS) were concentrated in the first year of life,
18 we compared case fatality rates for CHD hospital discharges in infants aged 1 year or
19 younger from 2001 to 2011. We found that, on average, fatalities were 3.6-fold higher in
20 infants with 22q11DS compared with the rate reported for CHD nationwide (Table 3).

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22 **The types of CHD in patients with 22q11DS tend to be more severe than those seen in**
23 **apparently isolated cases, thus we compared the fatality rates for specific cardiac defects**
24 **that are common in the syndrome.** We found that in patients with 22q11DS, the case-
25 fatality rate was 50% among the 22 patients with truncus arteriosus, 32% for the 75
26 patients with tetralogy of Fallot, 41% for the subgroup of 24 infants with tetralogy of Fallot
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Table 1. Causes of death according to the death certificate

	n	%
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Infection (pneumonia) or sepsis	7	11.9
Multisystem failure	2	3.4
Respiratory failure	1	1.7
Tracheobronchomalacia	1	1.7
Central nervous system anomaly	1	1.7
Unknown	1	1.7
TOTAL	59	100.0

Table 2. Univariate analysis of factors associated with mortality

Characteristic		Deceased, n (%)	Living, n (%)	TOTAL	p value (Fisher's exact test)	OR (95% CI) deceased vs. living patients
		59 (14.1)	360 (85.8)	419		
Gender	Male	26 (44.1)	172 (47.8)	198	0.67	0.87 (0.48-1.58)
	Female	33 (55.9)	188 (52.2)	221		
Cardiac status	CHD data available	52 (14.2)	314 (85.8)	366	<0.0001	5.27 (2.06-13.99)
	With CHD	46 (88.5)	187 (59.5)	233		
	Normal cardiac anatomy	6 (11.5)	127 (40.5)	133		
Calcium status	Calcium data available	24	253	277	0.001	4.27 (1.67-11.15)
	Hypocalcemia	15 (62.5)	71 (28.1)	86		
	Normal calcium	9 (37.5)	182 (71.2)	191		
Airway status	Airway data available	6	246	252	0.0043	13.38 (1.19-110.51)
	Malacia	4 (67)	32 (13)	36		
	Normal airway	2 (33)	214 (87)	216		

Table 3. Case fatality rates for hospital discharges in infants aged 1 year or younger with CHD: a comparison between patients with 22q11DS and the general national data (ICD 10 codes Q20-Q25).

Birth year	Case fatality rates in 22q11DS patients with CHD (per 100 cases)	General case fatality rate for CHD in Chile (per 100 cases)⁹	Ratio of case fatality for CHD in 22q11DS/general populations
2001	28.57	6.63	4.31
2002	18.18	8.53	2.13
2003	0.00	7.77	0.00
2004	23.81	9.29	2.56
2005	21.43	9.30	2.30
2006	30.00	6.79	4.42
2007	41.67	7.59	5.49
2008	29.41	6.63	4.43
2009	42.11	8.55	4.92
2010	33.33	6.78	4.92
2011	42.86	7.49	5.72
Average	28.31	7.75	3.65

DISCUSSION

Our observations confirm that patients with 22q11DS have high fatality rates. We found that 14.1% of a large cohort of Chilean patients, or 1 in 7, died during the 15-year observation period. For the subgroup of patients with the deletion and CHD, the fatality rate was 19.7% or almost 1 in 5 patients. To our knowledge, this is the largest series to report the case fatality rate and survival for this syndrome.

The majority of deaths occurred during the first year of life and were associated with the presence of CHD, particularly with severe cardiac defects that are common in this syndrome, such as tetralogy Fallot with pulmonary atresia and truncus arteriosus. Right-sided heart failure, which is related to pulmonary vascular resistance, a common complication of these anomalies, has been proposed as an important contributor to mortality^{3,11,12}.

The diagnosis and treatment of CHD has universal coverage under Chilean Health Care Reform¹³, and pediatric cardiac surgeries have been performed in 3 national referral centers since 2005. Therefore, it is unlikely that differences in local clinical practices are the main cause of the high mortality in patients with 22q11DS, at least in the past 8 years. In fact, similar figures have been observed in comparisons of the fatality rates before and after the implementation of universal coverage for CHD diagnosis and treatment, which was guaranteed after the health care reform. Although overall national infant mortality for CHD decreased during this period¹⁰, the impact of universal coverage is less evident for children with severe and complex defects, such as those that are present in patients with 22q11DS. Indeed, we found that patients with 22q11DS had a higher overall fatality rate compared with the national statistics for patients with similar CHDs but without the syndrome; this discrepancy was evident for specific cardiac defects that are common in the syndrome, such as tetralogy of Fallot, truncus arteriosus and VSD. This finding suggests that even for similar anatomic defects, there are additional manifestations and, most likely, other pathophysiologic features in patients with the syndrome that may contribute to higher fatality than is found in cases of apparently isolated defects. Among these features, we found that hypocalcemia and airway abnormalities were also significant risk factors associated with early death. Low calcium levels are common in patients with the deletion, particularly during the cardiac postoperative period. Shen et al.¹¹ determined that the frequency of hypocalcemia and the speed of calcium level decline after surgery is higher in patients with the deletion than in those without and that this difference is

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3 associated with postsurgical complications. The authors did not show an association
4 between hypocalcemia and mortality, as we did in our study, but this difference may be
5 related to their study's smaller sample size (n=19). We did not have parathyroid hormone
6 (PTH) levels for our patients, but other researchers have shown that postoperative
7 hypocalcemia is caused by a decreased PTH reserve^{11,14}. Our results emphasize a need
8 to direct specific attention to the calcium levels of 22q11DS patients during the
9 perioperative period.
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15 Airway malacia was also a risk factor for lethality. This manifestation can be caused by the
16 extrinsic compression by aberrant vessels or by intrinsic airway anomalies in 22q11DS
17 patients¹⁵. Its management often requires prolonged mechanical ventilation, which leads to
18 an increased risk of infection that may also contribute to mortality. Future studies of the
19 pathogenesis, early detection and management strategies of airway anomalies in the
20 syndrome will be relevant for treatment and prognosis.
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26 This study is limited by its retrospective nature, partially complete clinical data, including a
27 lack of accurate information about the timing of certain manifestations, such as
28 hypocalcemia, infections and mode of death, and biases related to the possible
29 underrecognition of an unknown proportion of patients with the deletion. Nevertheless, in
30 this relatively large series of patients, we found that the presence of 22q11DS adversely
31 affects survival, particularly in individuals with CHD, hypocalcemia and/or airway malacia.
32 There may be a need for modified surgical techniques, timing and/or perioperative
33 management of cardiac and extracardiac manifestations, as proposed by Carotti et al.¹⁶,
34 to improve survival in 22q11DS patients and make it at least comparable to their non-
35 syndromic counterparts, as is the current reality for patients with Down syndrome, for
36 example¹⁷.
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57 GL and PA participated in data acquisition. ID and HL performed the statistical analysis.
58 GMR, GL and CV and PA participated in the drafting and critical revision of the manuscript
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10 **Data sharing:** No additional data are available.
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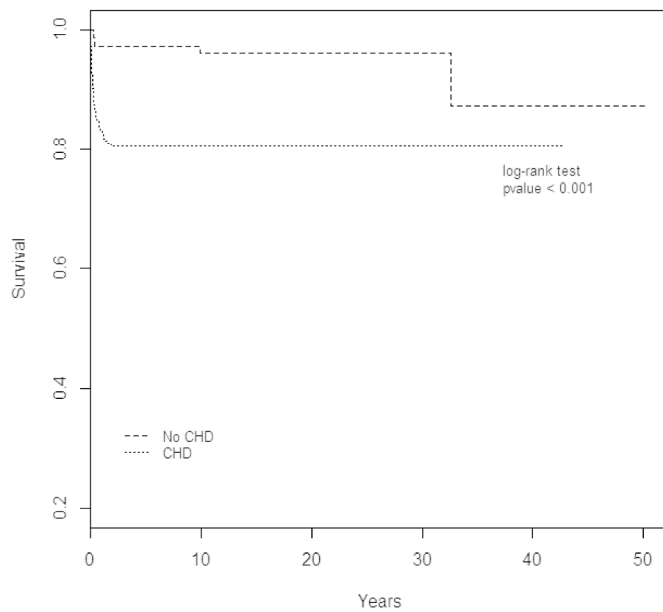
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Figure 1. Kaplan-Meier survival curves for 22q11DS patients with or without CHD



n, no CHD	133	91	31	15	7	1
n CHD	233	104	28	4	1	0
TOTAL	366	195	59	19	8	1

215x279mm (300 x 300 DPI)